UNIVERSIDADE ESTADUAL DE MONTES CLAROS

Vinícius Figueiredo Carneiro

HIPERTRICOSE ASSOCIADA ÀCONDIÇÕES GENÉTICAS RARAS: ASPECTOS CLÍNICOS

Montes Claros, Minas Gerais

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Área de Concentração: Aspectos clínicos dos cuidados em saúde.

Orientador: Prof. Hercílio Martelli Júnior
Coorientadora: Prof.ª Daniella Reis Barbosa Martelli

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“Na verdade só sabemos quão pouco sabemos – com o saber cresce a dúvida.”

GOETHE (1826)

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RESUMO

A hipertricose é caracterizada pelo aumento do crescimento capilar de caráter anormal para idade e sexo de um indivíduo, independente de andrógenos. A incidência da hipertricose isolada é desconhecida, sendo considerada rara. Essa incidência aumenta quando se apresenta como fenótipo de diversas alterações genéticas. A hipertricose pode ser um sinal cutâneo de uma doençagenética rara, que pode estar associada a malformações orgânicas múltiplas. O objetivo desse trabalho foi realizar um estudo das características clínicas das doenças genéticas raras associadas à hipertricose. Trata-se de um estudo de revisão crítica da literatura. Uma busca foi realizada no banco de dados *Online Mendelian Inheritance in Man* (OMIM), no período de junho de 2020 até outubro de 2020 para associações com os termos "*hipertricose"* e *"hirsutismo"*. Busca adicional foi realizada no banco de dados no Pubmed (https://pubmed.ncbi.nlm.nih.gov) e Orphanet (https://www.orpha.net/consor/cgi-bin/index.php)para complementação de artigos científicos.Os distúrbios não dependentes do metabolismo dos andrógenos ou com suspeita de acometimento concomitante foram incluídos como hipertricose. O envolvimento clínico de cada doença foi agrupado em categorias: cabeça e pescoço, herança genética, sistema esquelético, sistema cardiovascular, deficiência intelectual, sistema nervoso, neoplasia, sistema geniturinário, alterações do trato abdominal, sistema endócrino, sistema respiratório, morte precoce e anomalias dentárias. Para a avaliação dos distúrbios genéticos associados a hipertricose e anomalias dentárias utilizou-se a análiseSTRINGpara investigação de processos biológicos, vias e rede de interação proteína-proteína, com valor de p submetido à taxa de falsa descoberta para correção de vários testes, sendo considerados valores significativos ≤ 0,05.Cento e vinte e uma doenças genéticas raras associadas à hipertricose foram identificadas. O principal padrão de herança identificado foi autossômico recessivo (44,62%). As categorias mais afetadas foram cabeça e pescoço (80,16%), sistema esquelético (78,51%) e sistema nervoso (73,55%). Outras categorias que se destacaram foram deficiência intelectual (52,06%), abdome (42,97%), geniturinário (39,66%), anomalias dentárias (32,23%) e anomalias cardiovasculares (32,23%). Outras preocupações foram morte na infância (18,18%) e associação com neoplasias malignas (8,26%).Na avaliação das doenças genéticas associadas a hipertricose e anomalias dentárias, a agenesia foi encontrada em

41,02% dos distúrbios, seguido de atraso na erupção dentária(35,89%), espaçamento irregular(28,20%), entre outros. Genes causadores foram identificados em 33das39 síndromes genéticas. Dentre estes, foram relacionados 39 genes, dos quais 38 foram analizados pelo STRING, que evidenciou 148 processos biológicos e3 vias estatisticamente significativas. Tiveram maior significância estatística os processos biológicos desmontangem do nucleossomo (GO: 0006337, P=1.09e-06), organização cromossômica (GO: 0051276, P=1.09e-06) e remodelação de cromatina (GO: 0006338, P=7.86e-06)e as vias carcinoma hepatocelular (hsa05225, P=5.77e-05), termogênese (hsa04714, P= 0.00019) e ciclo celular (hsa04110, P=0.0433).O estudo mostra que a hipertricose pode ser uma sinalização para uma doença genética rara multissistêmica, e evidenciou os principais sistemas orgânicos envolvidos. As anomalias dentárias são marcadores de dismorfismo que podem auxiliar no processo diagnóstico. A análise STRING revelou os processos biológicos e as vias comuns aos pacientes com hipertricose e anomalias dentárias. O desenvolvimento de roteiro de orientações clínicas auxilia os profissionais de saúde, pacientes e seus respectivos familiares no cuidado com a saúde.

Palavras-chave: Hipertricose; Doenças Genéticas, Doenças Hereditárias, Transtornos Genéticos.

ABSTRACT

Hypertrichosis is characterized by excessive growth of hair, for an individual's age and sex, regardless of androgens. The incidence of isolated hypertrichosis is rare, but it increases when associated to the phenotype of several genetic disturbances. Hypertrichosis can be a cutaneous sign of a rare genetic disease, which can be associated to multiple organ malformations.It is a critical literature review study, with the objective to evaluate the clinicalcharacteristics of genetic diseases associated with hypertrichosis. A search was conducted in the *Online Mendelian Inheritance in Man* (OMIM) from June 2020 to October 2020 for associations with the terms "*hirsutism"*and*"hypertrichosis*". Additional search was performed in Pubmed (https://pubmed.ncbi.nlm.nih.gov)and Orphanet (https://www.orpha.net/consor/cgi-bin/index.php)for complemental scientific articles. Non-dependent disturbancesto androgen metabolism or syndromes with overlapping features were included as hypertrichosis. Clinical involvement of each disease were evaluated into categories as features of head and neck, inheritance pattern, skeletal, cardiovascular, intellectual disability, nervous system, neoplasia, genitourinary, abdominal, endocrine, respiratory tract, early death and dental anomalies.For the evaluation of genetic syndromes associated with hypertrichosis and dental anomalies, STRING, analysis of functional enrichment of protein-protein interaction networks, was used to investigate biological processes, pathways and interaction network of the genetic diseases associated with hypertrichosis and dental anomalies. The p values were subjected to the false discovery rate for correction of several tests, and values ≤ 0.05 were considered significant.One hundred twenty-one rare genetic conditions associated with hypertrichosis were identified. The main inheritance pattern was autosomal recessive (44.62%). The most affected categories were head and neck features (80.16%), skeletal system (78.51%) and nervous system (73.55%). Other affected categories highlighted were intellectual disability (52.06%), abdomen (42.97%), genitourinary (39.66%),dental anomalies (32.23%) and cardiovascular abnormalities (32.23%). Additional major concerning were early death (18.28%) and association with malignancies (8.26%). In the evaluation of genetic diseases associated with hypertrichosis and dental anomalies, agenesis was

found in 41.02% of the disorders, followed by delayed in tooth eruption (35.89%) and widely spaced teeth (28.20%), among others.Causative genes were identified in 33 out of 39genetic syndromes. Among them, 39 genes were relatedand 38were analized by STRING, wich showed 148 biological processes and 3 pathwaysstatistically significant. The most significant biological processes were disassembly of the nucleosome (GO: 0006337, p=1.09e-06), chromosomal organization (GO: 0051276, p=1.09e-06) and remodeling of the chromatin (GO: 0006338, p=7.86e-06), and the pathways were hepatocellular carcinoma (hsa05225, p=5.77e-05), thermogenesis (hsa04714, p=0.00019) and cell cycle (hsa04110, p=0.0433).The study shows that hypertrichosis may be a clue to a rare multisystemic genetic disease, and correlates the main organ systems involved.Dental anomalies in patients with hypertrichosis associated with genetic diseases are a marker of dysmorphism that can assist in the investigative process.The STRING analysis evidenced the biological processes and pathways common to patients with hypertrichosis and dental anomalies.The development of a clinical guidelines script assists health professionals, patients and their respective family members in health care.

Keywords: Hypertrichosis; Genetic Diseases; Hereditary Disease; Inborn Genetic Disease.

LISTA DE ABREVIATURAS E SIGLAS

ACTH	Hormônio adrenocorticotrófico
Bmps	Proteínas morfogenéticas ósseas
CID-11	Classificação Estatística Internacional de Doenças e Problemas
CONITEC	Comissão Nacional de Incorporação de Tecnologia no Sistema Único de Saúde
DHEA	Dehidroepiandrosterona
EUA	Estados Unidos da América
EURORDIS	Aliança européia não governamental sobre doenças raras
FAEC	Fundo de Ações Estratégicas e Compensação
IGF-1	Fator de crescimento semelhante a insulina 1
MHC	Complexo principal de histocompatibilidade
Msx2	Homeobox do segmento muscular
NGF	Fator de crescimento do nervo neurotrofina
NORD	Organização Nacional de Desordens Raras dos Estados Unidos da América
OMIM	Online Mendelian Inheritance in Man
PCDT	Protocolos Clínicos e Diretrizes Terapêuticas
SAI/SUS	Sistema de Informação Ambulatorial/Sistema Único de Saúde
SDHEA	Sulfato de dehidroepiandrosterona
SGK3	Soro e glicocorticoide responsivo a quinase 3
Shh	*Sonic hedgehog*
SUS	Sistema Único de Saúde
TGF- β	Fator de crescimento transformador β
Wnts	Via de sinalização
α-MSH	Hormônio estimulador de melanócitos alfa

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SUMÁRIO

1. INTRODUÇÃO

Hipertricose é o excesso de crescimento de pelos de caráter anormal para idade e sexo de um indivíduo, em qualquer lugar do corpo (WENDELIN; POPE; MALLORY, 2003). É diferente de hirsutismo, que significa crescimento de pelos terminais em mulheres e crianças, em topografia dependente de andrógeno, em locais onde geralmente não há pelos terminais. Estes crescem em um padrão de distribuição típico de adulto masculino.Pelos terminais são habitualmente vistos em face, tórax, abdome e costas dos homens(ROSENFIELD, 2005).

A hipertricose pode ser consequência de várias causas:uso de medicamentos, doenças genéticas, distúrbios metabólicos ou não-endócrinos, mas não é causada por excesso de andrógenos. Apesar disso, os andrógenos podem agravar o problema (HOHL; RONSONI; OLIVEIRA, 2014).

O primeiro caso documentado da literatura científica foi o caso de Petruz Gonzales, nascido no arquipélago das Ilhas Canárias em 1556, no Castelo de Ambras (GARCIA-CRUZ; FIGUERA; CANTU, 2002). Outros casos ficaram famosos na literatura, como exibicionistas em circo, exemplificado pelo caso da Julia Pastrana, uma dançarina mexicana de origem indígena, e pelo russo Theodoro Petrov (BONDESON; MILES, 1993). Aspectos históricos remontam desde a passagem bíblica no Velho Testamento, livro de Genesis 25:25 “E saiu o primeiro ruivo e todo como um vestido de pelo; por isso chamaram o seu nome Esaú” (BÍBLIA, GÊNESIS, 25:25).

Trata-se de uma doença rara, cuja incidência isoladamente é desconhecida. Estima-se uma incidência de 1 em 1 bilhão de indivíduos para a forma hereditária da doença (FANTAUZZO *et al*; 2012; BEIGHTON, 1970). A incidência aumenta quando a hipertricose está incluída no fenótipo de diversas alterações genéticas (GARCIA-CRUZ; FIGUERA; CANTU, 2002).

Não há uma definição universalmente aceita para doenças raras. A maioria das definições tende a considerar a prevalência, embora outras consideram a severidade ou seu caráter hereditário (BADYAL, 2006). A ausência consensual de uma terminologia adequada pode resultar em confusão e, consequentemente, dificultar o acesso do paciente ao tratamento(RICHTER *et al*., 2015).

A Ata de Doenças Raras de 2002, nos Estados Unidos da América (EUA), define doença rara de acordo com sua prevalência, especificamente qualquer doença ou condição que afeta menos de 200.000 pessoas; no Japão, é a condição que atinge menos de 50.000 ou cerca de 1 em 2.500 indivíduos; na União Europeia, menos de 5 em 10.000 indivíduos da população geral(ALAWI, 2019). Segundo a Organização Mundial de Saúde (OMS) e o Ministério de Saúde do Brasil (MS), doença rara é a doença cuja prevalência afeta até 65 pessoas em cada 100.000 indivíduos, ou seja, 1,3 para cada 2.000 indivíduos (BRASIL, 2021).

Há cerca de 8.000 tipos de doenças raras, das quais estima-se que 80% tenha origem genética(MARTELLI; MARTELLI JÚNIOR, 2020). São doenças crônicas, progressivas, muitas sem cura, podem ser incapacitantes e levar ao óbito, afetando significativamente os indivíduos acometidos e suas respectivas famílias. Embora sejam individualmente consideradas raras, acometem um percentual significativo da população quando consideradas em conjunto, o que resulta em um problema de saúde relevante (BRASIL, 2021). É estimado 13 a 15 milhões de pessoas com doenças raras no Brasil (MARTELLI; MARTELLI JÚNIOR, 2020).

1.1 Morfogênese do folículo piloso

O desenvolvimento do folículo piloso ocorre durante a evolução da pele fetal e envolve interações coordenadas entre células mesenquimais e epiteliais (SCHNEIDER; SCHMIDT-ULLRICH; PAUS, 2009). A formação do folículo piloso pode ser dividida em oito estágios distintos, caracterizados pela indução do folículo piloso, organogênese e citodiferenciação ou maturação. O desenvolvimento do folículo piloso humano começa entre a 8ª e 12ª semana de gestação(BLUME-PEYTAVI *et al*., 2008).

O estágio 1 é quando ocorre o espessamento do epitélio primitivo, que induz as células mesenquimais a povoarem a pele para formar a derme colágena subjacente (SCHMIDT-ULLRICH; PAUS, 2005). Os primeiros placódios do folículo piloso são vistos nas regiões da sobrancelha, lábio superior e queixo. No estágio 2, a formação do placódio ectodérmico se expande e inicia a penetração na derme. No estágio 3, o placódio dá lugar a um folículo piloso no estágio inicial de fixação. Os folículos pilosos crescem na derme em um ângulo com a superfície da pele, com o grau do ângulo determinado pela localização do folículo piloso (PINKUS, 1958). A fase 4, ou fase bulbosa, ocorre por

volta de 12ª a 14ª semanas de gestação, quando a base epitelial do cabelo no couro cabeludo se invagina para envolver os condensados de células dérmicas e formar papilas dérmicas (HARDY, 1969).

Entre os estágios 4 e 5, um núcleo de células epiteliais se separa das células epiteliais periféricas, que mais tarde se tornam a bainha externa da raiz, contínua com o epitélio não folicular. O núcleo da célula epitelial, repousando no topo da papila dérmica, se diferencia na bainha da raiz interna de Henle, Huxley e camadas de cutícula, e o núcleo central das células da matriz dão origem à cutícula da fibra capilar, córtex e medula(BREATHNACH; ROBINS, 1981).

No estágio 5, período da gestação entrea 13ª e16ª semanas, as porções superficiais dos folículos pilosos desenvolvem duas protuberâncias de células distintas no lado "posterior" do folículo: a protuberância superior mais próxima da superfície da pele forma a glândula sebácea, enquanto a protuberância inferior forma a localização das células-tronco foliculares e mais tarde ancorará o músculo eretor do pelo. O próprio músculo eretor do pelo se desenvolve independentemente do folículo piloso e geralmente é visto pela primeira vez na derme próximo à glândula sebácea em desenvolvimento (PINKUS, 1958).

Os folículos pilosos se diferenciam no segundo trimestre, e formam as sete camadas de células em cilindros concêntricos vistos em folículos pilosos maduros. O estágio 6 é definido pelo desenvolvimento e crescimento visível da fibra capilar. O estágio 7 ocorre por volta de 19ª a 21ª semanas de gestação, quando se formam os canais capilares. No estágio 8, os folículos capilares estão totalmente formados e as primeiras fibras capilares emergem da pele (BLUME-PEYTAVI *et al*., 2008).

O cabelo lanugo inicial da primeira fase de crescimento do cabelo da fase anágena cresce até 24ª a 28ª semanas de gestação. O desenvolvimento dos folículos pilosos progride na direção cefalocaudal e, quando há cabelos longos na face e couro cabeludo, muitas áreas do tronco e das extremidades apresentam fios de cabelo dentro das bainhas celulares ou fios parcialmente protuberantes na epiderme (HOLBROOK; ODLAND, 1978).

1.2 Ciclo do cabelo

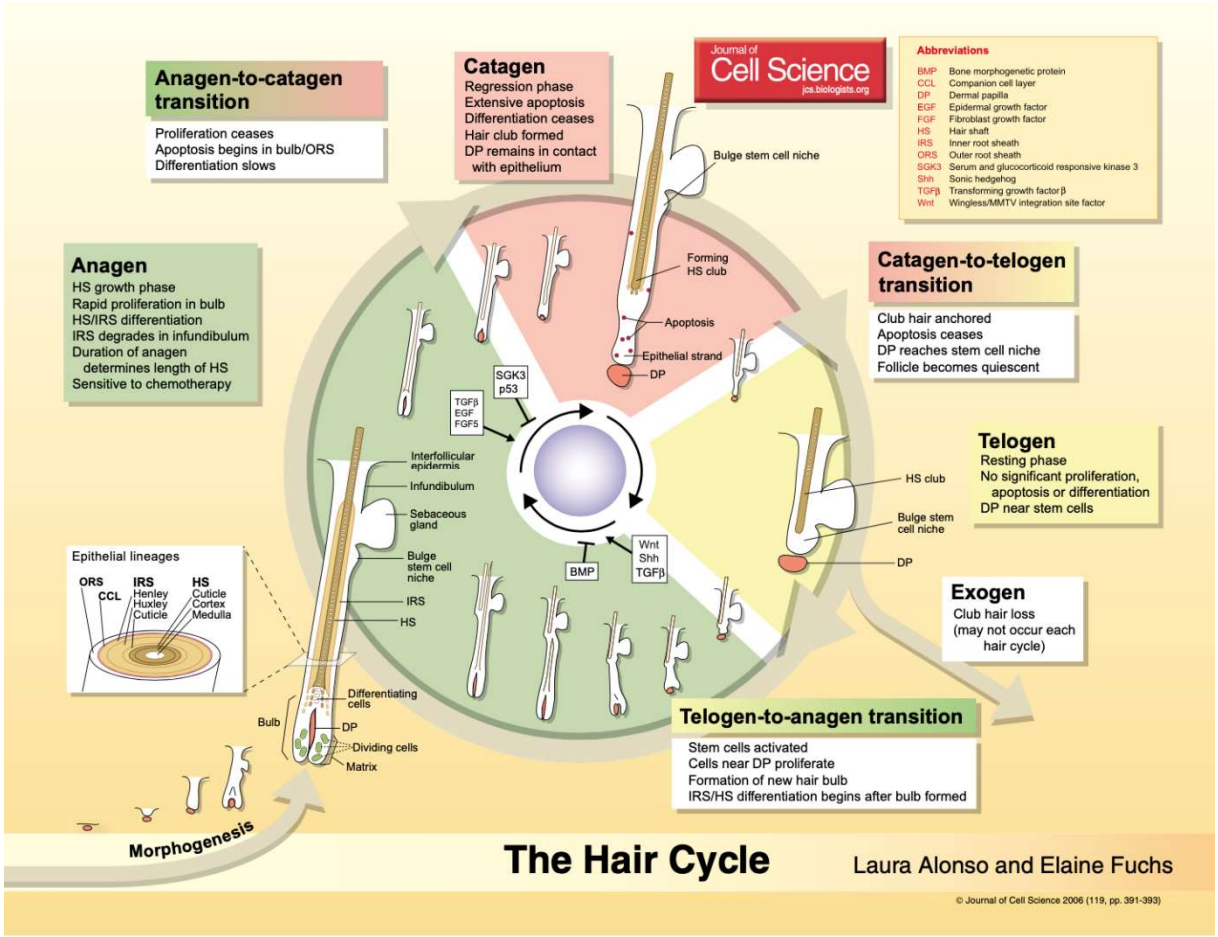
A atividade cíclica do folículo piloso é tradicionalmente dividida em fase de crescimento (anágena), fase de regressão (catágena) e fase de repouso (telógena), conforme a figura 1. Alguns autores caracterizam a queda capilar como um processo ativo, denominado exógeno. O período de intervalo até que o ciclo novamente se inicie com uma fase anágena é denominado kenogênio (STENN, 2005; ALONSO; FUCHS, 2006).

Os eventos de morfogênese e atividade cíclica do folículo piloso são controlados por uma rede complexa de sinalização, por meio de citocinas, hormônios, neurotransmissores e seus receptores, fatores de transcrição e enzimas, que agem via endócrina, parácrina ou autócrina. O ciclo do cabelo é paralelo à morfogênese, que inclui remodelação e regeneração de toda a porção não permanente do folículo capilar (ALONSO, FUCHS, 2006).

Na fase anágena, os folículos são angulados para permitir que o pelo fique plano ao longo da superfície do corpo, embora sejam longos e retos. As células da matriz em proliferação têm uma duração do ciclo celular de aproximadamente 18 horas (LAVKER *et al*., 2003). As células crescem para cima e irão se diferenciar nas linhagens da bainha radicular interna (Henley, Huxley e cutícula) e as camadas da haste do cabelo (cutícula, córtex e medula) (HARLAND, 2018).

Todas as células do folículo piloso apresentam taxa proliferativa aumentada, com a maior atividade observada nas células da matriz. A papila dérmica determina o tamanho do bulbo anágeno e sua duração, determinando o diâmetro da haste capilar, a taxa de crescimento do cabelo e o comprimento máximo da fibra capilar (ELLIOTT; STEPHENSON; MESSENGER, 1999). Não está claro o que determina a duração da fase anágena nas células da papila dérmica, mas são sugeridas hipóteses que envolvem um relógio bioquímico (PAUS; FOITZIK, 2004). Fatores conhecidos por manter o anágeno incluem SGK3 e Msx2 (ALONSO *et al*., 2005; MA *et al*., 2003).

Figura 1. Ciclo do folículo piloso



Fonte: ALONSO; FUCHS, 2006.

A próxima fase é denominada catágena, transição entre anágeno e telógeno (MULLER-ROVER *et al.,* 2001). É uma fase que dura 2 a 3 semanas, na qual o bulbo capilar migra da hipoderme para a derme média. É caracterizada por apoptose das células da matriz capilar, com interrupção da produção de proteína e pigmento, e involução da parte inferior do folículo. Durante o catágeno, a porção inferior de cada folículo capilar regride em um processo que inclui apoptose de células epiteliais no bulbo e na bainha radicular externa (LINDNER *et al*., 1997). O resultado final é a formação de uma fita epitelial, um remanescente do folículo piloso, que funciona para aproximar a papila dérmica da protuberância (HSU; PASOLLI; FUCHS,2011).

Na fase telógena, o folículo piloso regride até cerca da metade de seu tamanho anterior e não se estende além da derme superior. As células epiteliais do folículo telógeno

inferior não apresentam síntese significativa de DNA ou RNA, nem há síntese de proteínas características do folículo anágeno (ALONSO; FUCHS, 2006).

A fase exógena é o período em que ocorre a queda da fibra capilar por um processo ativo controlado, o que difere da quiescência da fase telógena (STENN, 2005). A morfologia da raiz do cabelo sugere que o processo exógeno envolve um evento proteolítico que ocorre entre as células móveis da base do eixo telógeno. A queda de cabelo geralmente ocorre quando o folículo entra novamente em uma nova fase anágena (STENN, 2005).

Kenogênio é o intervalo após o telógeno e antes que se inicie um novo folículo anágeno. A transição do telógeno para o anágeno ocorre quando células-tronco quiescentes na base do folículo telógeno são ativadas para produzir uma nova haste capilar (BLANPAIN *et al*., 2004). A destruição das células-tronco foliculares resulta em alopecia cicatricial (STENN, 2005). Vias de sinalização por Wnts (LOWRY *et al*., 2005; VAN MATER *et al*., 2003) e Shh (CALLAHAN *et al*., 2004) são indispensáveis para o novo anágeno, enquanto Bmps (KULESSA; TURK; HOGAN, 2000) foram implicados na diferenciação do folículo.

A duração das diferentes fases do ciclo capilar depende do tipo e da localização do folículo piloso. A duração da fase anágena é a principal determinante do comprimento máximo do cabelo. A fase anágena dos folículos capilares do couro cabeludo geralmente persiste por 2 a 6 anos, embora alguns indivíduos possam ter fases de crescimento anágeno de duração mais longa. Na puberdade, os cabelos vellus das áreas dependentes de androgênio se transformam em cabelos terminais sob influência hormonal: aos 7a 9 anos,no púbis e axila, e aos 12 a 14 anos,na face(COURTOIS*et al*., 1996). Neste contexto, o comprimento máximo e a taxa de crescimento do cabelo terminal variam nas diferentes regiões do corpo (tabela 1).

Os cabelos do couro cabeludo crescem cerca de 0,3mm/dia e podem atingir um comprimento de mais de um metro. O comprimento máximo do cabelo diminui com a idade. Em contraste, o cabelo da sobrancelha cresce apenas a uma taxa de 0,1 mm/dia e tem uma fase anágena de 2 a 3 meses (PAUS; COTSARELIS, 1999).

Tabela 1.Características dos folículos pilosos relacionado à sua localização

Localização	*Estágio de crescimento*	*Tempo de duração*
Couro cabeludo	Anágena	2-6 anos
	Catagena	2-3 semanas
	Telógena	3 meses
Barba	Anagena	4-14 semanas
	Telogena	10-18 semanas
Braços	Anágena	6-12 semanas
	Telogeno	7-13 semanas
Pernas	Anágena	19-26 semanas
	Telógena	13-34 semanas

Fonte: BLUME-PEYTAVI *et al.,* 2008.

1.3 A unidade pilosebácea

A presença de pelos é característica dos mamíferos, nos quais exercem uma ampla gama de funções: proteção física, isolamento térmico, camuflagem, dispersão de suor e sebo, funções sensoriais e táteis e interações sociais. Folículos pilosos ocorrem em todo o corpo humano, exceto nas palmas das mãos, solas dos pés, prepúcio glabro e lábios. Em humanos adultos, existem dois tipos principais de folículos: folículos terminais, encontrados no couro cabeludo, e folículos vellus, que são mais abundantes em face e tronco (COTSARELIS; BOTCHKAREV, 2008). O cabelo é composto de queratinócitos mortos, terminalmente diferenciados, que são compactados em uma fibra de incrível resistência à tração (SCHNEIDER; SCHMIDT-ULLRICH; PAUS, 2009).

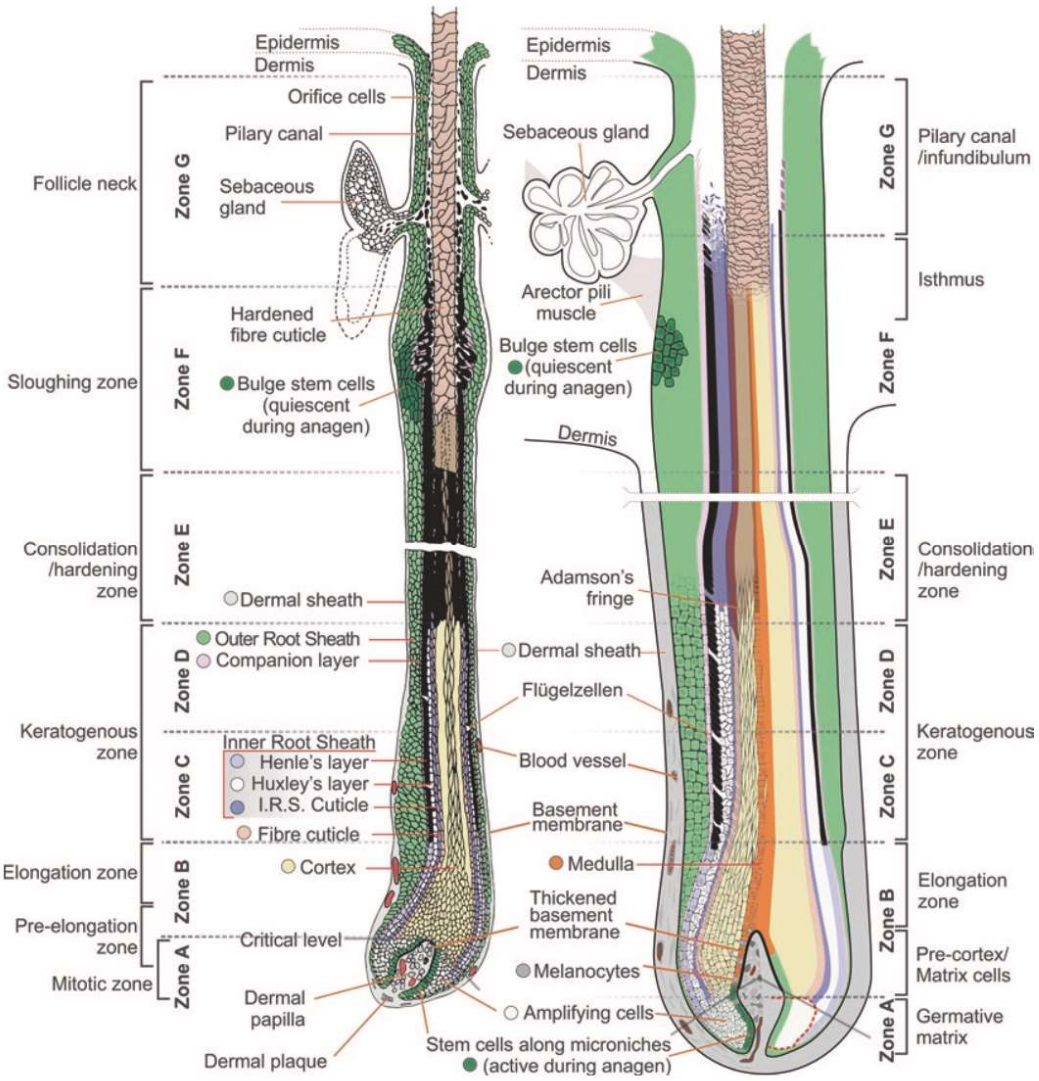
Embora os folículos tenham características estruturais e de desenvolvimento semelhantes, seu tamanho e forma variam de acordo com a localização do corpo e suas características funcionais, com apresentação morfológica bastante heterogênea (SCHNEIDER; SCHMIDT-ULLRICH; PAUS, 2009). Podem ser identificados folículos capilares produtores de cabelo lanugo, folículos capilares vellus, folículos capilares

intermediários e folículos capilares terminais. A unidade pilosebácea é constituída pelo folículo piloso, a glândula sebácea e o músculo eretor do pelo, conforme a figura 2.

O desenvolvimento do folículo piloso é regulado por vários fatores de crescimento, citocinas, neuropeptídeos e hormônios, que em parte são produzidos pelo próprio folículo piloso. No entanto, o ciclo do folículo piloso é um fenômeno autônomo que pode continuar mesmo em folículos pilosos isolados em cultura (STENN; PAUS, 2001).

As células-tronco do folículo piloso ectodérmico dão origem a todos os componentes epiteliais do folículo piloso, incluindo a glândula sebácea e a glândula apócrina, enquanto as células derivadas do mesoderma se desenvolvem na papila dérmica folicular e na bainha de tecido conjuntivo. Os progenitores de melanócitos derivados da crista neural dão origem à unidade pigmentar do folículo piloso (FUCHS, 2008).

Figura 2. Unidade pilosebácea



Fonte: HARLAND, 2018.

O bulbo anágeno contém os queratinócitos da matriz e a unidade pigmentar do folículo piloso. A extremidade inferior do infundíbulo é marcada pela inserção do ducto da glândula sebácea. A linha divisória fica abaixo da região do bojo e da inserção do músculo eretor do pelo, o local potencial de células-tronco epiteliais (HARLAND, 2018).

Na extremidade proximal, o infundíbulo se junta à região do istmo da bainha externa da raiz, onde o músculo eretor do pelo é inserido. A região do bojo, situado no istmo inferior, abriga células-tronco do folículo piloso epitelial e melanocítico. Embora o infundíbulo, o istmo, a protuberância e o bulbo capilar têm origem ectodérmica, a papila dérmica é derivada do mesoderma (HARLAND, 2018).

O bulbo capilar é a porção profunda do folículo piloso que envolve a papila dérmica. Esta é uma parte permanente da base do folículo, que contém a matriz capilar que produz a haste do cabelo e suas lâminas (PAUS; COTSARELIS, 1999). O crescimento do cabelo resulta da atividade proliferativa dos queratinócitos da matriz no bulbo, que fica na papila dérmica, um condensado de células mesenquimais especializadas com propriedades indutivas (WOO; ORO, 2011).

Todo o epitélio do folículo piloso é circundado por uma bainha de tecido conjuntivo derivada do mesoderma, um acúmulo frouxo de colágeno e células estromais repousando sobre uma membrana basal (BLUME-PEYTAVI *et al*., 2008).O folículo piloso é circundado por uma densa rede de vasos sanguíneos, terminações nervosas e populações de células especializadas, incluindo melanócitos, células neuroendócrinas e células do sistema imunológico (PAUS *et al*., 2006).

1.4 Tipos de folículo piloso

Existem quatro tipos de folículo piloso: lanugo, vellus, intermediário e terminal.As características respectivas de cada um estão descritas na tabela 2. Os folículos capilares podem ser diferenciados de acordo com sua estrutura e pelo tempo de aparecimento no corpo, sendo que um folículo pode mover-se de uma categoria para outra (ROOK, 1965).

Tabela 2. Características dos tipos de folículo piloso.

Tipo de cabelo	***Características***
Lanugo	<30μm diâmetro; >2mm comprimento
Vellus	<30μm diâmetro; <2mm comprimento
Intermediário	>30<60μm diâmetro; >2mm comprimento
Terminal	>60μm diâmetro; >2mm comprimento

Fonte: BLUME-PEYTAVI *et al.,* 2008.

O folículo lanugo é o primeiro crescimento capilar, produzido na fase intrauterina, e é eliminado após o nascimento. É caracterizado por ser fino, macio, pouco pigmentado e não medulado. Também pode ser observado em adultos com várias formas de hipertricose (DE BERKER; MESSENGER; SINCLAIR, 2004). A presença de pelo lanugo por todo o corpo no momento do parto pode ser um sinal de prematuridade (BLUME-PEYTAVI *et al*., 2008).Após o nascimento, subsequente ao crescimento do lanugo, é observado o folículo intermediário. É caracterizado por uma cutícula áspera, com pigmentação esparsa e medula fragmentada ou ausente (BLUME-PEYTAVI *et al*., 2008).

Os folículos vellus são não medulados, finos e mal pigmentados. Eles penetram na derme papilar, mas não na camada de gordura subcutânea (WENDELIN; POPE; MALLORY, 2003). Como uma característica morfológica, este tipo capilar frequentemente exibe estrutura epitelial semelhante a saia ou cápsula de tecido conjuntivo perifolicular, com um espaço claro entre a bainha externa da raiz e essa estrutura semelhante a saia, ou entre a bainha externa da raiz e a cápsula de tecido conjuntivo perifolicular. Este espaço é preenchido por uma substância mucinosa rica em terminações nervosas perifoliculares e, entre outros tipos de células, contém fibroblastos alongados e mastócitos (NARISAWA; HASHIMOTO; KOHDA, 1995). Estes folículos continuam a crescer ao longo da vida, mesmo em áreas consideradas como tendo apenas cabelos terminais, como o couro cabeludo, e podem constituir 7% a 25% dos cabelos presentes (BLUME-PEYTAVI *et al*., 2008).

O cabelo terminal é pigmentado, medulado e tem diâmetro maior em comparação com os outros tipos de fibra capilar. Tem haste mais larga que a bainha da raiz interna do folículo, alcança a derme profunda e seu bulbo está localizado na gordura subcutânea(WENDELIN; POPE; MALLORY, 2003). Este folículo cresce em comprimento, sendo que o tamanho e forma do cabelo variam com a localização e função no corpo. Os cílios têm o maior diâmetro de todos os pelos do corpo, forte pigmentação, uma fase de crescimento ativo relativamente curta e podem proteger os olhos contra fluidos e poeira (MONTAGNA; PARAKKAL, 1974).

1.5 Fatores endócrinos, neurológicos e imunológicos

O folículo piloso é local de intensa interação com o meio ambiente. É um apêndice da pele densamente inervado e tem relações bidirecionais com a malha de terminações nervosas e células do sistema imunológico. Enquanto neuromediadores e neuropeptídeos são capazes de influenciar o crescimento do cabelo, os queratinócitos do folículo piloso produzem fator de crescimento do nervo (NGF) e outros fatores neurotróficos que induzem a remodelação de inervação da pele de uma maneira dependente do ciclo do cabelo (FIOTZIK *et al.,* 2006).

Células apresentadoras de antígenos podem ser encontradas em elevada densidade na pele com folículo piloso, sobretudo em sua porção superior, onde são encontrados na camada suprabasal e na camada basal da bainha radicular externa (THOMAS *et al*., 1984). Entretanto, os compartimentos do folículo capilar transitório apresentam um número muito baixo de células imunes (CHRISTOPH *et al.,* 2000).

As células-tronco da crista neuroectodérmica, que podem dar origem a melanócitos imaturos, foram identificadas na região do bojo. Os melanócitos situam-se na zona da matriz e direcionam a pigmentação da fibra capilar, por meio da transferência dos melanossomas para os queratinócitos, atividade dependente do ciclo capilar. A densa malha perifolicular das terminações nervosas sensoriais está intimamente associada aos mastócitos, células endoteliais e macrófagos (SLOMINSKI *et al.,* 2005).

Mediadores neuroendócrinos, incluindo substância P, cortisol, ACTH, CRH, POMC e neurotrofinas, todos expressos no folículo piloso, exercem efeitos moduladores do crescimento do cabelo (PAUS *et al.,* 2006). Entretanto, os reguladores mais importantes do cabelo humano são os andrógenos, desde que haja boa nutrição e função tireoidiana normal (RANDALL, 2007).

Os andrógenos regulam o crescimento do cabelo humano e seus efeitos variam dependendo da localização do corpo. Os folículos capilares em regiões do corpo como o rosto, a axila, o púbis e o tórax estão sujeitos ao efeito estimulador dos andrógenos. Os folículos capilares localizados nos cílios não estão sob a influência de andrógenos (BLUME-PEYTAVI *et al*., 2008).

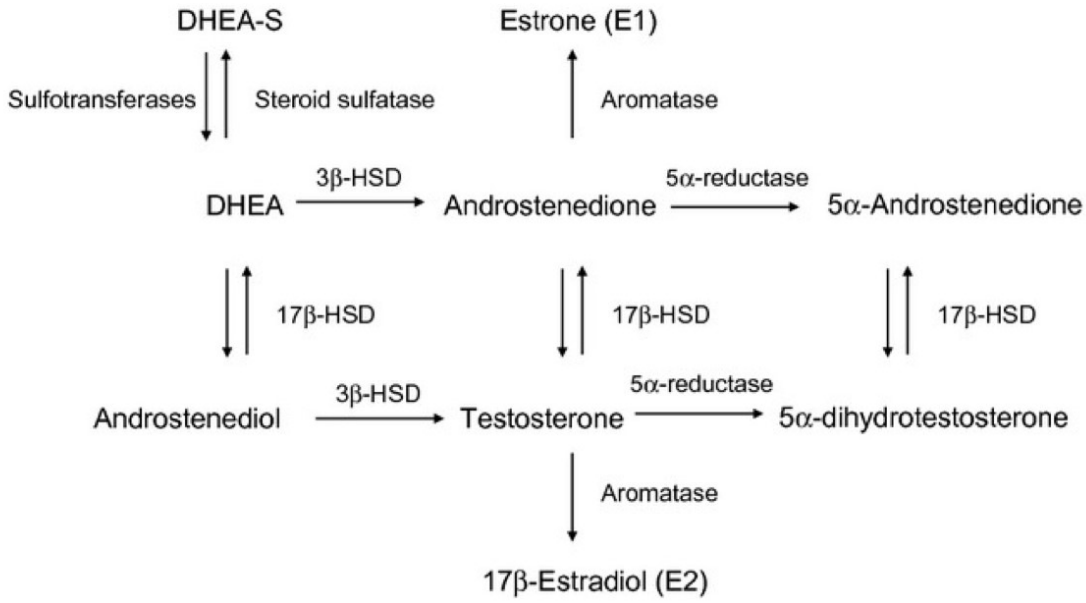
O folículo capilar é um órgão dinâmico capaz de regenerar fios novos e diferentes de acordo com a regulação hormonal para coordenar o tipo de cabelo com a estação, idade ou sexo. Antes da puberdade, existem apenas pelos vellus nas áreas púbica e axilar de homens e mulheres.Entretanto, quando os andrógenos aumentam na puberdade, os folículos capilares se tornam terminais, com o desenvolvimento de pelos púbicos e axilares em ambos os sexos, ocorrendo mais cedo em meninas do que em meninos (MARSHAL; TANNER, 1969; MARSHAL; TANNER, 1970).

Nos homens, a testosterona é produzida principalmente pelos testículos a partir da puberdade. Nas mulheres em idade reprodutiva, é produzida pelo córtex adrenal e ovários,sendo sintetizada em grande parte pela conversão da androstenediona. Os andrógenos fracos,dehidroepiandrosterona (DHEA) e sulfato de dehidroepiandrosterona (SDHEA), são produzidos principalmente no córtex adrenal. A androstenediona é produzida em quantidades equivalentes no córtex adrenal e ovários, e em menor quantidade pelos testículos. Esses andrógenos fracos, como DHEA, DHEA-S e androstenediona são convertidos em andrógenos mais potentes na pele, por meio das glândulas sebáceas, glândulas sudoríparas e células da papila dérmica (ZOUBOULIS*et al.,* 2007).

A pele e as unidades pilosebáceas contêm uma gama de enzimas relacionadas ao metabolismo dos andrógenos(CERUTI; LEIROS; BALANA, 2018), conforme disposto na figura 3. A enzima 5α-redutase é responsável pela conversão de testosterona em di-hidrotestosterona, um androgênio mais potente, em tecidos como a pele, folículos pilosos, próstata, vesículas seminais, fígado e cérebro (HOFFMANN *et al.,* 2001).

As enzimas aromatase, 17 beta-hidroxisteróide desidrogenase (17 β-HSD) e 5α-redutase (tipo I e II) estão localizados na bainha externa da raiz, ao passo que dentro da bainha interna estão localizadas as enzimas aromatase e 5α-redutase (tipo I e II). A papila dérmica é o local de ação das enzimas aromatase, 17 β-HSD, 5α-redutase (tipo II) e sulfatase (CERUTI; LEIROS; BALANA, 2018).

Figura 3Metabolismo dos andrógenos na pele



Fonte: INUI; ITAMI, 2012.

Os andrógenos agem nas células-alvo ligando-se a receptores intracelulares específicos (CHATURVEDI; DEHM, 2019). Em alguns tecidos, como o músculo esquelético, a testosterona se liga ao receptor. No entanto, em outros tecidos, como a próstata, a testosterona é metabolizada intracelularmente por uma das enzimas 5α-redutase em 5α-dihidrotestosterona, que se liga preferencialmente e mais fortemente ao receptor de andrógeno para ativar a expressão gênica (HANDELSMAN, 2005).

A 5α-redutase tipo 1 é detectada em vários órgãos independentes de androgênio, como fígado e cérebro, enquanto 5α-redutase tipo 2 é predominantemente observada em órgãos dependentes de androgênio, como epidídimo e próstata (RUSSELL *et al.,* 1994). Os sinais-chave identificados incluem fator de crescimento semelhante à insulina-1 (IGF-1) na estimulação do crescimento do folículo piloso e fator de crescimento transformador-β (TGF-β) na inibição (INUI; ITAMI, 2013).

A influência dos andrógenos, contudo, é um paradoxo biológico:estimulam o folículo piloso em muitas áreas, não têm efeito em outras e pode ter efeito oposto em outra parte do corpo, inclusive no mesmo indivíduo.Assim, nos homens, os andrógenos estimulam o crescimento da barba, mas podem ter efeito contrário, suprimindo o crescimento do cabelo na alopecia androgenética (RANDALL, 2007). Nas mulheres é possível

encontrar perda de cabelo semelhante, andrógeno-dependente, mas o padrão é diferente, pois a linha do cabelo frontal é normalmente mantida e ocorre um afinamento generalizado progressivo no vértice (LUDWIG, 1977).

Todos os folículos dependentes de andrógeno requerem resposta do respectivo receptor de andrógeno, como demonstrado pela ausência de pelos do corpo adulto em completa insensibilidade andrógena. Dessa maneira, indivíduos XY com insuficiência androgênica completa desenvolvem um fenótipo feminino (MCPHAUL, 2005). Entretanto, o fenótipo feminino é incompleto, pois não desenvolvem nem mesmo os padrões femininos de pelos pubianos ou axilares. O hormônio do crescimento também é necessário para a resposta androgênica completa, pois o desenvolvimento dos pelos sexuais é inibido na deficiência de hormônio do crescimento (RANDALL, 2007).

Pseudo-hermafroditas masculinoscom deficiência de 5α-redutase tipo 2 produzem apenas padrões femininos de crescimento de pelos pubianos e axilares após a puberdade, embora suas formas corporais se tornem masculinizadas (WILSON; GRIFFIN; RUSSELL, 1993).Não obstantenenhum ou pouco crescimento de barba e nenhuma alopecia androgenética seja identificada, indicando que 5α-redutase tipo 2 é necessária para o crescimento de barba e desenvolvimento de alopecia androgenética, a própria testosterona pode estimular a axila e folículos do triângulo púbico inferior, característicos de mulheres adultas(RANDALL, 2007).

Os folículos necessitam da exposição aos andrógenos para as transformações iniciais, mas não necessariamente para manter seus efeitos. Se os homens são castrados, o crescimento da barba diminui, mas nem o crescimento da barba nem a calvície de padrão masculino retornam aos níveis pré-púberes, sugerindo que parte da expressão do gene alterado não requer andrógenos para manter seus efeitos (HAMILTON, 1958). Outro aspecto interessante observado é que a resposta androgênica original do folículo transplantado é mantida no receptor, o que aponta ao fato de que os folículos de diferentes áreas podem ter expressões gênicas diferentes, uma vez que todos estão expostos aos mesmos hormônios circulantes (ORENTREICH; DURR, 1982).

1.6 Patogênese da hipertricose

Há várias teorias para a patogênese da hipertricose. Um dos mais importantes mecanismos propostos é a conversão do cabelo intermediário ou vellus em cabelo terminal. Durante a puberdade, a produção de andrógeno faz os folículos crescerem, aprofundarem na derme e converterem em cabelo terminal. Acontecimento semelhante se faz na hipertricose, porém em regiões que usualmente não teriam cabelo terminal (STENN; PAUS, 2001). Outro mecanismo importante envolvido na hipertricose envolve os ciclos do crescimento do cabelo, que sofrem influência sistêmica dos andrógenos, hormônios tireoidianos e hormônio do crescimento. A hipertricose ocorre quando folículos passam mais tempo na fase de crescimento do que o esperado para sua localização (EBLING, 1987). Um terceiro mecanismo, menos estabelecido, seria o aumento na densidade folicular na hipertricose. Entretanto, apesar dos mecanismos envolvidos na patologia serem conhecidos, o gatilho para o seu desencadeamento é pouco compreendido (EBLING, 1987).

1.7 Classificação

A hipertricose é classificada de acordo com a idade de início (congênita ou adquirida), extensão de distribuição (generalizada ou localizada) e se isolada ou associada a outras anormalidades (POLIZZI *et al*., 2005).A hipertricose é classificada no CID 11, conforme a tabela 3.

Tabela 3 - CID 11 – versão 09/2020

CID 11 – versão 09/2020
ED71 – Hipertricose
9A04.Y Outras desordens adquiridas específicas dos cílios • Hipertricose da pálpebra
9B70 Distrofia da retina herdada

• Amaurose – Hipertricose
LC30 Defeitos do desenvolvimento do cabelo ou crescimento do cabelo
• Hipertricose nevóide
EC21.4 Hipertricose determinada geneticamente
EH72.Y Outras anormalidades do cabelo induzidas por medicamentos específicos
• Hipertricose induzida por medicamento
EL10 Síndromes paraneoplásicas envolvendo a pele
• Hipertricose lanuginosa adquirida
LD27.0Y Outras síndromes de displasia ectodérmicas especificas
• Hipertricose com fibromatose gengival
LD27.3 Síndromes genéticas com Hipertricose
LD2F.1Y Outras síndromes especificas com anomalias múltiplas estruturais, sem origem ambiental
• Querubismo – fibromatose gengival – epilepsia – deficiência mental – hipertricose – crescimento atrofiado (Ramon) síndrome

Fonte: CID 11

1.8 Aspectos de política pública sobre doenças raras

Desde a década de 80do século XX, tem crescido o reconhecimento de que as doenças raras são um importante problema médico e social. Em 1983, foi criado nos EUA a Organização Nacional de Desordens Raras (NORD), que foi fundamental para a aprovação da *Orphan Drug Act* - Lei de incentivo ao Desenvolvimento de Drogas Orfãs - para o tratamento das doenças raras(SOUZA *et al*., 2019).

Na Europa, desde a década de 90 do século XX, a organização European Organization for Rare Diseases (EURORDIS) tem ganhado novos adeptos a cada ano, com participação de 106 países em 2021 (RAREDISEASEDAY, 2021).Em 2008, a EURORDIScriou o dia comemorativo mundial das doenças raras (*rare disease day*), no último dia do mês de fevereiro, escolha realizada pela irregularidade característica desse dia (RAREDISEASEDAY, 2021).Em 2005, foi realizada a primeira Conferência Internacional sobre Doenças Raras e Medicamentos Órfãos. Em 2009, o Brasil organizou o I Congresso Brasileiro de Doenças Raras, mesmo ano em que foi instituída

a Política Nacional de Atenção Integral em Genética Clínica(SOUZA *et al*., 2019).

A legislação vigente sobre doenças raras encontra-se na Portaria Nº 199, DE 30 DE JANEIRO DE 2014, que instituiu a Política Nacional de Atenção Integral às Pessoas com Doenças Raras, aprovou as Diretrizes para Atenção Integral às Pessoas com Doenças Raras no âmbito do Sistema Único de Saúde (SUS) e estabeleceu incentivos financeiros de custeio, e também na PORTARIA Nº 1.559, DE 1º DE AGOSTO DE 2008, que crioua Política Nacional de Regulação do Sistema Único de Saúde – SUS (BRASIL, 2021).

A partir de 2016, o Ministério da Saúde habilitou estabelecimentos de saúde para funcionarem como Serviços de Referência para Doenças Raras integrados ao SUS, sendo que, até 2019, eram oito centros (localizados em Anápolis/GO, Distrito Federal, Recife/PE, Curitiba/PR, Rio de Janeiro/RJ, Porto Alegre/RS, Santo André/SP e Salvador/BA).No ano de 2021, o serviço de referência foi ampliado para dezessete centros especializados em doença rara (foram acrescentados mais uma unidade em Salvador/BA, duas unidades em Fortaleza/CE, Vitoria/ES, Brasília/DF, Belo Horizonte/MG, Florianópolis/SC, Campinas/SP e Ribeirão Preto/SP) –relacionados na tabela4 (BRASIL, 2021).

A assistência aos indivíduos com doenças raras segue as diretrizes gerais de atenção estabelecidas pelo SUS, embora muitas doenças não tenham protocolos próprios. O Ministério da Saúde disponibiliza Protocolos Clínicos e Diretrizes Terapêuticas (PCDT) para doenças raras, documentos estes que orientam os profissionais de saúde na prevenção, diagnóstico, tratamento e reabilitação dos pacientes (BRASIL, 2021).Ressalta-se que a Política Nacional de Atenção Integral às Pessoas com Doenças Raras organiza, desde 2014, essa rede de atendimento. Este documento tem como objetivo melhorar o acesso aos serviços de saúde e à informação, reduzir a incapacidade causada por essas doenças e contribuir para a melhoria da qualidade de vida das pessoas com doenças raras. Além disso, também agrupou as doenças raras em eixos de acordo com suas características comuns, devido ao grande número de doenças raras existentes, o que impossibilitaria de ser realizado de forma individual. Os eixos são estruturados em origem genética e origem não genética (BRASIL, 2021).

Tabela 4. Centros de tratamento de doenças raras no Brasil

UF	Município	Estabelecimento
DF	Distrito Federal	Hospital de Apoio de Brasília
GO	Anápolis	Associação de Pais e Amigos dos Excepcionais
PE	Recife	Associação de Assistência a Criança deficiente
PR	Curitiba	Hospital Pequeno Príncipe de Curitiba
RJ	Rio de Janeiro	Instituto Fernandes Figueira
RS	Porto Alegre	Hospital das Clínicas de Porto Alegre
SP	Santo André	Ambulatório de Especialidade da Faculdade de Medicina ABC
BA	Salvador	Associação de Pais e Amigos Excepcionais
BA	Salvador	Hospital universitário prof. Edgard Santos – HUPES
CE	Fortaleza	Hospital Universitário Walter Cantídio
CE	Fortaleza	Hospital Infantil Albert Sabin
ES	Vitória	Hospital Santa Casa de Vitoria
DF	Brasília	Hospital Materno Infantil de Brasília
MG	Belo Horizonte	Hospital Infantil Joao Paulo II
SC	Florianópolis	Hospital Infantil Joana de Gusmão
SP	Campinas	Hospital das Clínicas de Campinas
SP	Ribeirão Preto	Hospital das Clínicas de Ribeirão Preto

Fonte: BRASIL, 2021.

As de origem genética são dividas em: 1-Anomalias Congênitas ou de Manifestação Tardia; 2- Deficiência Intelectual; 3- Erros Inatos do Metabolismo. As de origem não genética são divididos em 1- Infecciosas; 2- Inflamatórias; 3- Autoimunes; 4- Outras Doenças Raras de Origem não Genética. Acrescenta-se a isso que aincorporação de novas tecnologias, seja na prevenção, diagnóstico ou tratamento da doença, envolve a análise dos estudos científicos pela Comissão Nacional de Incorporação de Novas Tecnologias do Ministério da Saúde (CONITEC) (BRASIL, 2021).

Por consequente, esses pacientes são atendidos prioritariamente pela Atenção Básica, principal porta de entrada para o SUS e, em caso de necessidade, são encaminhados para atendimento especializado em Unidade de Média e Alta Complexidade, em

conformidade com a Rede de Atenção à Saúde (BRASIL, 2021).

O financiamento é realizado pelo Fundo de Ações Estratégicas e Compensação (FAEC), repassado aos Estados, Distrito Federal e Municípios a partir da publicação da Portaria de Habilitação dos Serviços e/ou Serviços e Produção dos respectivos procedimentos no Sistema de Informação Ambulatorial (SIA/SUS), para os procedimentos com fins diagnósticos em doenças raras. O financiamento também conta com recursos próprios dos gestores em cada competência, Federal, Estadual ou Municipal, para assistência e cuidado em saúde(BRASIL, 2021).

A hipertricose é uma característica clínica pouco valorizada no exame físico, no entanto, pode sinalizar uma doença genética rara, com acometimento de vários sistemas orgânicos.
Este estudo visa realizar um levantamento das doenças genéticas raras associadas a hipertricose e avaliar a frequência das manifestações clínicas das síndromes estudadas.

2. OBJETIVOS

2.1 Objetivo Geral

Avaliar os aspectos clínicosdas síndromes genéticas raras associadas a hipertricose.

2.2 Objetivos Específicos

- Realizar o levantamento das doenças genéticas associadas à hipertricose.
- Avaliara frequência dos grupos de acometimento clínico nas doenças genéticas raras associadas a hipertricose.
- Avaliar as anomalias dentárias em síndromes genéticas raras associadas a hipertricose.

3. METODOLOGIA

3.1 Delineamento do estudo

Tratou-se de um estudo do tipo revisão crítica da literatura.

3.2 Coleta de dados

Para realização deste estudo, foram coletadas informações em bancos de dados de acesso público *Online Mendelian Inheritance in Man* (OMIM), para associações com os termos "*hypertrichosis*" *e* "*hirsutism"*. Quando não foi observado dependência com o metabolismo dos andrógenos, como hiperandrogenismo ou condições relacionadas, os distúrbios foram incluídos como hipertricose. Síndromes com acometimento concomitante também foram incluídos na pesquisa. Uma busca adicional foi realizada no Pubmed e Orphanet para complementação de artigos científicos. As características de cada distúrbio foram coletadas e organizadas emgrupos de acometimento clínico: cabeça e pescoço, herança genética, sistema esquelético, sistema cardiovascular, sistema nervoso, deficiência intelectual, neoplasia, sistema geniturinário, trato abdominal, sistema endócrino, trato respiratório, morte precoce e anomalias dentárias.As anomalias dentárias foram agrupadas de acordo com a classificação estabelecida por De La Dure-Molla *et al* (2019).

3.3 Análise de dados

Os dados coletados foram lançados no Excel para construção do banco de dados e para realização da distribuição de frequências das categorias de acometimento clínico. Foi realizado uma análise STRING (SZKLARCZYK *et al.*, 2021) para as doenças com hipertricose e anomalias dentárias.

3.4 Aspectos éticos

O estudo coletou dados de domínio público, dispensando a aprovação do Comitê de Ética e Pesquisa, seguindo as diretrizes e normas da Resolução nº 466/2012 do Conselho Nacional de Saúde que regulamenta a ética em pesquisa.

4. PRODUTOS

Em consonância com o Regulamento Interno do Programa de Pós-graduação em Cuidado Primário em Saúde, os resultados do presente estudo serão apresentados na forma de artigo científico e produto técnico.

4.1. Produtos Científicos

4.1.1 Artigo Científico

"***A*** *review of genetic syndromes associated with hypertrichosis*" – Aprovado para publicação na *Revista da Associação Médica Brasileira.*

4.1.2 Artigo Científico

"*Dental anomalies in syndromes displaying hypertrichosis in the clinical spectrum*"– formatado e submetido para a Revista: *World Journal of Stomatology.*

4.2 Produto Técnico

4.2.1 Vídeo informativo - Pitch

4.1.1 Artigo Científico 1

A review of genetic syndromes associated with hypertrichosis

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Conflict of interest
None declared.

Ethical approval
Not required.

Patient consent
Not required.

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A review of genetic syndromes associated with hypertrichosis

Abstract

Hypertrichosis is characterized by an increase in hair growth beyond normal variation in areas that are not predominantly androgen-dependent. In addition to being a cosmetic problem, cutaneous manifestations can hide multiple organ system anomalies. A search was performed in the online electronic database *Online Mendelian Inheritance in Man* for the terms "*hypertrichosis*" and "*hirsutism*", and genetic entities with hypertrichosis were included. Additional searches were performed in Pubmed and Orphanet to catalogue scientific articles relevant to each genetic condition. The clinical involvement of each disease was evaluated into categories as features of the head and neck, inheritance, skeletal, cardiovascular, intellectual disability, nervous system, neoplasia, genitourinary, abdominal, endocrine, respiratory tract, early death and dental anomalies. One hundred twenty-one rare genetic conditions associated with hypertrichosis have been identified. The main inheritance pattern was autosomal recessive (44.62%). The most affected categories observed were head and neck features (80.16%), skeletal (78.51%), and nervous system (73.55%). Other highlighted categories were intellectual disability (52.06%), abdomen (42.97%), genitourinary (39.66%), dental anomalies (32.23%), cardiovascular (32.23%), respiratory (25.61%), early death until childhood (18.18%), endocrinophaties (14.04%), and malignancies (8.26%). This study shows that hypertrichosis may hide an underlying systemic genetic disease and highlighted the most affected organ systems. This topic requires further investigation.

Keywords: Hypertrichosis; Genetic Diseases; Hereditary Disease; Genetic Disease, Inborn.

Introduction

Hypertrichosis can be very troublesome for the affected patients and their families. This condition is characterized by an increase in hair growth beyond normal

variation in areas that are not predominantly androgen-dependent, independent of age, race, or sex[1,2]. Hypertrichosis is classified according to the age of onset (congenital or acquired), extent of distribution (generalized or localized), and whether it is isolated or associated with various abnormalities[2,3].Further classification takes into consideration the type of follicle: lanugo, vellus, or terminal hair. Lanugo follicles are responsible for the growth of the first hairs, which are thin, soft, slightly pigmented, and not medullated, produced in the uterus and are eliminated after birth. Lanugo hypertrichosis has been observed in adults with various forms of hypertrichosis.Vellus follicles are not medullated, thin, poorly pigmented, and terminal hair is pigmented, medullated, and has a larger diameter compared to other types of hair [1,4].

The incidence of isolated hypertrichosis is unknown, and it is considered very rare. The incidence increases when it presents itself as a phenotype of several genetic syndromes[2]. Several causes of hypertrichosis have been described, including the use of drugs, infection, neoplasia, genetic diseases, and metabolic or non-endocrine disorders, but is not caused by an excess of androgens[5]. This condition is often confused with hirsutism; however, the latter refers specifically to growth of terminal hair in women or children, in androgen-dependent areas, in places where there is normally no terminal hair, with a typical adult male distribution pattern[6].

There are several theories for the pathogenesis of hypertrichosis. First, it has been proposed to be caused by the conversion of intermediate or vellus hair to terminal hair, or from changes in the hair growth cycles, with follicles spending more time in the anagen phase and an increase in follicular density[1].However, the triggers of these mechanisms are still not fully understood.

Hypertrichosis is not only a cutaneous sign, it can also indicate an underlying rare complex disease that can affect multiple organ systems[1-3,7], and has previously been related to abnormalities in the head and neck, skeletal, nervous system, intellectual disability, neoplasia, abdominal, genitourinary, cardiovascular, among others. However, there are only a few reviews in the literature. The aim of the present study was to offer an overall survey of hypertrichosis-associated genetic diseases described in the literature and provide a summary of its clinical presentation.

Material and methods

A search was performed from June 2020 to October 2020 in the online electronic

database *Online Mendelian Inheritance in Man* (OMIM, https://www.omim.org), with associations of the terms "*hypertrichosis*" or "*hirsutism*."Non-dependent disturbances to androgen metabolism or syndromes with overlapping features were included as hypertrichosis.Additional searches were performed in the electronic databases PubMed (https://pubmed.ncbi.nlm.nih.gov) and Orphanet (https://www.orpha.net/consor/cgi-bin/index.php) to complement the search for scientific articles, in English language.

The clinical features of each disturbance were organized into categories by one collaborator, as provided in OMIM: features of the head and neck, inheritance, skeletal, cardiovascular, intellectual disability, nervous system, neoplasia, genitourinary, abdominal, endocrine, respiratory, dental anomalies andphenotypic and genetic characteristics were also evaluated. The data were entered into Excel forstatistical analyses. The study collected public domain data, thus dispensing with the approval of the Ethics and Research Committee.

Results

Two hundred seventy-four entries were found in OMIM. In 33 entries, both terms hypertrichosis and hirsutism were referring to the same disturbance. One hundred twenty-one genetic conditions associated with hypertrichosis were included in the research, described in Chart 1. Were excluded description of genes and disturbances caused by hyperandrogenism or related conditions, such as polycystic ovarian syndrome, hyperprolactinemia, hyperthyroidism, congenital adrenal hyperplasia, androgen-secreting tumors, among others. However, more than one OMIM entry can refer to the same syndrome. Disturbances with overlapping syndromeswere also included. A few disturbances weren't found in OMIM, but were found in Pubmed: (dysraphism, nevoid hypertrichosis, polythelya pilosa, primary multifocal hypertrichosis and segmental odontomaxillary dysplasia). The distribution of the frequency of clinical involvement categories is described in Table 1.

The main inheritance pattern observed was autosomal recessive (44.62%). Nevertheless, some disturbances can occur with a mixed pattern.Autossomal dominant was observed in 36.36% and other or unknown inheritance patterns were observed in 20.66% of genetic entities.The most affected categories observed were the head and neck features (80.16%), skeletal (78.51%) and the nervous system (73.55%).

Other highlighted categories were intellectual disability (52.06%), abdomen

(42.97%), genitourinary (39.66%), dental anomalies (32.23%), cardiovascular (32.23%), respiratory (25.61%) and early death, until childhood (18.18%). Malignancies were another concern, observed in 8.26% of cases, as described in Table 2, and endocrinopathies were identified in 14.04% of disturbances.

Discussion

There has been a growing recognition that rare diseases are relevant medical and social problems[8-10].In this study, one hundred twenty-one genetic disturbances associated with hypertrichosis were identified. The first documented case of hypertrichosis in the scientific literature was the case of Petruz Gonzales, born in the Canary Islands archipelago in 1556, at the Ambras Castle[2].Other cases later became famous, including those of circus exhibitionists, such as the case of Julia Pastrana, a mexican dancer of indigenous origin, and the russian Theodoro Petrov[11,12].Although more than 300 new Mendelian phenotypes are added to the OMIM each year[13], only a few cases of hypertrichosis associated genetic disturbances have been reported.

The prevalence of hypertrichosis congenital generalized is very rare [2]. Nevertheless, no universally accepted definition for rare diseases has yet been established [10,14]. According to the World Health Organization (WHO) and the criterion adopted by the Ministry of Health of Brazil, a rare disease is a disease whose prevalence affects less than 65/100,000 individuals or 1.3/2000 individuals[15,16].All conditions described in this study are rare.

Hypertrichosis can be classified as being associated with other symptoms, or as an isolated feature, but there are only a few examples of hypertrichosis as a cardinal symptom [17].The majority of diseases express hypertrichosis as a component of complex syndromes [18], as shown in this study. Another classification is based on the localization hypertrichosis; however, the literature is not always clear enough to discern between localized and generalized hypertrichosis.

Head and neck features were the most affected category, identified in more than two-thirds of the disturbances; this includes abnormalities in the head, face, ears, eyes, nose, mouth, neck, and teeth, which reveal the importance of a thorough physical exam. Teeth abnormalities were identified in 32.23% of genetic entities. Dental anomalies are excellent dysmorphic markers and may help in syndrome diagnosis[12,19].

Skeletal involvement was identified in 78.51% of disturbances. Genetic skeletal

disorders account for most human skeletal dysplasia; however, the genotype-phenotype correlations remain an important challenge[20]. Mutations in the same gene may be associated with heterogeneous phenotypes, as the same phenotype can be caused by mutations in several genes, such as Coffin-Siris, which has a wide genetic heterogeneity[20].

The nervous system was affected in 73.55% of the genetic entities. Intellectual disability (ID) is a prominent feature observed in 52.06% of cases, usually identified early in childhood, due to developmental delay[7]. Given the greater clinical severity of the disease, its incidence is much higher than the worldwide prevalence, estimated at 1% of the general population[21]. ID is diagnosed by IQ testing; however, its severity (mild, moderate, severe, and profound) can be highly variable, even in the same disorder, given the wide heterogeneous phenotype of genetic diseases[21].

Another major concern is the association between hypertrichosis and cancer development, observed in 8.26% of cases (Table 2). In this context, different genes are associated, the main inheritance pattern observed is autosomal dominant, and the prognosis is usually poor. No correlation was found between the genetic entity and a unique type of malignancy, as one condition can be associated with several types of malignancies, but some may occur more often than others. For example, melanocitic nevus syndrome is associated with melanoma, and Beckwith-Wiedemann is associated with Wilm's tumor and hepatoblastoma[22,23]. Nevertheless, Bloom syndrome and Shinzel-Giedion syndrome are associated with multiple malignancies[24,25]. In other genetic diseases, such as the Boring-Opitz syndrome and Rubinstein-Taybi syndrome, tumor predisposition has been observed in many case reports, but the risk cannot be established or fully dismissed because epidemiologic studies have not been conducted to demonstrate an increased risk of developing cancer[26,27].

Hypertrichosis is not caused by androgens, but is often confused with hirsutism, which is usually associated with hyperandrogenism. In this study, 17 conditions were associated with endocrinophaties. The most common abnormalities were diabetes mellitus, insulin resistance, and thyroid dysfunction (hypothyroidism and thyroid lymphangiectasis). Diabetes mellitus, insulin resistance, and acanthosis nigricans type A and Donohue syndrome are caused by a mutation in the insulin receptor gene (INSR) and are associated with insulin resistance and hyperinsulinemia. [28,29]Another example is the Bernardinelli-Seip syndrome, which is associated with polycystic ovary disease

and diabetes mellitus and the Beckwith-Widemann syndrome, which is associated with adrenocortical cytomegaly and pituitary hyperplasia[23,30]. However, the Donohue syndrome, Bernardinelli-Seip syndrome and Beckwith-Widemann syndrome are the major causes of hypertrichosis in the literature[1,2,18,23]. One probable reason why these genetic conditions are classified as hypertrichosis is that hyperandrogenism may aggravate the problem, as hypertrichosis has also been described in adult males, not only in androgen dependent-areas[1,2,18].

Hypertrichosis can cause a significant emotional distress for affected patients and their families[1,18]. Patients may experience difficulty in accessing the qualified health system, as the clinical characteristics are heterogeneous and can lead to diagnosis delays[15]. Early diagnosis of these conditions helps guide early intervention, screening, and genetic counseling of patients and their family members. The development of clinical protocols helps health professionals, patients, and families to make decisions regarding the most appropriate alternatives for their health care.

There is a limitation in the interpretation of data from case reports, with a small number of patients, an inherent characteristic of rare disease studies. The literature is not always clear enough to elucidate the type of hair disorder, whether hypertrichosis or hirsutism. Indeed, it is common for both terms to be used in case reports of the same genetic disorder. It was imperative to deepen the knowledge to perform the necessary discernment to conduct the work and exclude what was not the object of investigation of the study.

Conclusion

This study shows that hypertrichosis may be more common than estimated, especially when we consider it to be a phenotype of several diseases. The research also suggested that cutaneous manifestations may also hide an underlying disease that requires investigation. Multiple organ systems can be affected, and the study highlights the most affected ones. These aspects reinforce the need for further studies to support protocols for public organizations and policies, facilitate decision-making, and promote ongoing health training for the management of hypertrichosis and its underlying potential disorders.

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References

[1] Wendelin DS, Pope DN, Mallory SB. Hypertrichosis. J Am Acad Dermatol. 2003; 48(2):161–79

[2] Garcia-Cruz D, Figuera LE, Cantu JM. Inherited hypertrichoses. Clin Genet. 2002; 61(5):321–9.

[3] Polizzi A, Pavone P, Ciancio E, La Rosa C, Sorge G, Ruggieri M. Hypertrichosis cubiti (hairy elbow syndrome): a clue to a malformation syndrome. J Pediatr Endocrinol Metab. 2005; 18(10):1019-25.

[4] Stenn KS, Paus R. Controls of hair follicle cycling. Physiol Rev. 2001; 81(1):449-94.

[5] Hohl A, Ronsoni MF, Oliveira MD. Hirsutism: diagnosis and treatment. Arquivos Brasileiros de Endocrinologia & Metabologia. 2014; 58(2):97-107.

[6] Rosenfield RL. Clinical practice. Hirsutism. N Engl J Med. 2005; 353(24):2578–88.

[7] Pezzani L, Milani D, Tadini G. Intellectual Disability: When the Hypertrichosis Is a Clue. J Pediatr Genet. 2015; 4(3):154-8.

[8] Harari S. Why we should care about ultra-rare disease. Eur Respir Rev. 2016; 25(140):101-3.

[9] Wastfelt M, Fadeel B, Henter JI. A journey of hope: lessons learned from studies on rare diseases and orphan drugs. J Intern Med. 2006; 260(1):1–10.

[10] Martelli DRB, Martelli Júnior H. Undiagnosed and rare diseases: current challenges, perspectives and contribution of oral cavity examination. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020; 130 (2):227-228.

[11] Maranda EL, Fipps D, Danek D, Taneja R, Marsh AM, Jimenez JJ. Dermatologic Marvels-Hypertrichosis. JAMA Dermatol. 2016 May 1; 152(5):552.

[12] Bondeson J, Miles AE. Julia Pastrana, the nondescript: an example of congenital, generalized hypertrichosis terminalis with gingival hyperplasia. Am J Med Genet. 1993; 47(2):198–212.

[13] Hartley T, Balci TB, Rojas SK, Eaton A, Canada CR, Dyment DA, et al. The unsolved rare genetic disease atlas? An analysis of the unexplained phenotypic descriptions in OMIM. American Journal of Medical Genetics. Part C, Seminars in Medical Genetics. 2018; 178(4), 458–463.

[14] Richter T, Nestler-Parr S, Babela R, et al. Rare Disease Terminology and Definitions-A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group. Value Health. 2015; 18(6), 906–914.

[15] Brazil. Ministry of Heatlh. Rare diseases. [cited 2021 Fev 02] Available from: http://portalms.saude.gov.br/saude-de-a-z/doencas-raras.

[16] Martelli-Júnior H. In Reply to: Alawi F. Using rare diseases as teaching models to increase awareness [Letter to the editor]. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019; 128(6):690-1.

[17] De Raeve L, Keymolen K. Congenital hypertrichosis lanuginosa in a father and son. Arco. Derm. 2011; 147(6):746-747.

[18] Pavone P, Praticò AD, Falsaperla R, Ruggieri M, Zollino M, Corsello G, et al. Congenital generalized hypertrichosis: the skin as a clue to complex malformation syndromes. Ital J Pediatr. 2015; 41:55.

[19] Bloch-Zupan A. When neuropediatrics meets odontology. Neuropediatrics. 2007; 38(2):57-8

[20] Geister KA, Camper SA. Advances in Skeletal Dysplasia Genetics. Annu. Rev. Genomics Hum. Genet. 2015; 16:199–227.

[21] Vissers LE, Gilissen C, Veltman JA. Genetic studies in intellectual disability and related disorders. Nat Rev Genet. 2016; 17(1):9-18

[22] Kinsler VA, Thomas AC, Ishida M, Bulstrode NW, Loughlin S, Hing S, et al. Multiple congenital melanocytic nevi and neurocutaneous melanosis are caused by postzygotic mutations in codon 61 of NRAS. J. Invest. Derm. 2013; 133(9):2229-2236.

[23] Zollino M, Orteschi D, Marangi G, De Crescenzo A, Pecile V, Riccio A, et al. A case of Beckwith-Wiedemann syndrome caused by a cryptic 11p15 deletion encompassing the centromeric imprinted domain of the BWS locus. J Med Genet. 2010; 47 (6):429-432.

[24] Ellis NA, German, J. Molecular genetics of Bloom's syndrome. Hum. Molec. Genet. 1996; 5:1457-1463.

[25] Hoischen A, Van Bon BWM, Gilissen C, Arts P, Van Lier B, Steehouwer M, et al. De novo mutations of SETBP1 cause Schinzel-Giedion syndrome. Nature Genet. 2010; 42(6):483-485.

[26] Hennekam RCM. Rubinstein-Taybi syndrome. Europ. J. Hum. Genet. 2006; 14(9):981-985.

[27] Hoischen A, Van Bon BWM, Rodriguez-Santiago B, Gilissen C, Vissers LELM, Vries, P, et al. De novo nonsense mutations in ASXL1 cause Bohring-Opitz syndrome. Nature Genet. 2011; 43(8):729-731.

[28] Mariani S, Pedone A, Meschi F, Di Natale B, Caputo R, Brogg U,Chiumello, G.Insulin resistance in a child with acanthosis nigricans type. Acta Paediat. Scand. 1982; 71(4):667-670.

[29] Cantani A, Ziruolo MG, Tacconi ML. A rare polydysmorphic syndrome: leprechaunism--review of forty-nine cases reported in the literature. Ann. Genet. 1987; 30(4):221-227.

[30] Garg, A. Acquired and inherited lipodystrophies. New Eng. J. Med. 2004; 350(12):1220-1234.

Chart 1. Genetic syndromes associated with hypertrichosis.

Syndromes	
Achalasia-Microcephaly	Dental Anomalies And Short Stature
Adducted Thumbs Syndrome	Desanto-Shinawi Syndrome
Agenesis of corpus callosum, cardiac, ocular and genital syndrome	Developmental and Epileptic Encephalopathy 57
Alazami-Yuan Syndrome	Developmental and Epileptic Encephalopathy 85 With or Without Midline Brain Defects
Amaurosis Congenita, Cone-Rod Type, With Congenital Hypertrichosis	Diabetes Mellitus, Insulin Resistant, With Acanthoses Nigricans Type A
Anemia, Congenital Hypoplastic, With Multiple Congenital Anomalies/Mental Retardation Syndrome	Diarrhea, chronic, with villous atrophy
Barber-Say Syndrome	Distichiais, Tristichiasis
Becker Nevus Syndrome	Donohue Syndrome
Beckwith-Wiedemann Syndrome	Dysraphism
Bloom Syndrome	Dyssegmental Dysplasia, Rolland-Desbuquois Type
Bohring-Opitz Syndrome	Ectodermal Dysplasia 14, Hair/Tooth Type with or Without Hypohidrosis
Cahmr Syndrome	Ehlers-Danlos Syndrome, Dermatosparaxis Type
Cantu Syndrome	Erythroderma, Ichthyosiform, Congenital, Reticular
Cerebellar Ataxia, Mental Retardation, And Dysequilibrium Syndrome 2	Erythrokeratodermia Variabilis Et Progressiva 2
Cerebellar, Ocular, Craniofacial, And Genital Syndrome	Facial Dysmorphism, Hypertrichosis, Epilepsy, Intellectual/Developmental Delay, And Gingival Overgrowth Syndrome
Cerebral Malformation, Seizures, Hypertrichosis, And Overlapping Fingers	Facial Hypertrichosis
Cerebrooculofacioskeletal Syndrome 1	Fibromatosis, Gingival, With Hypertrichosis And Mental Retardation
Cervical Hypertrichosis with Underlying Kyphoscoliosis	Filippi Syndrome
Cervical Hypertrichosis, Anterior Cervical	Floating-Harbor Syndrome
Cervical Hypertrichosis, Congenital Anterior Cervical, with Peripheral Sensory and Motor Neuropathy	Fontaine Progeroid Syndrome
Chromosome 17q12 Deletion Syndrome	Frontometaphyseal Dysplasia 1 e 2
Chromosome 17q21.31 Duplication Syndrome	GM-1- Gangliosidosis type I
Coffin-Siris Syndrome 1, 2, 3, 4, 8 ,9	Hairy Ears; Hairy Ears, Y-Linked
Congenital Disorder Of Glycosylation Iaa, Iq e IIe	Hairy Elbows
Cornelia De Lange Syndrome 1, 3, 4	Hairy Palms and Soles
Corpus Callosum, Agenesis Of, With Abnormal Genitalia	Hajdu-Cheney Syndrome
Cousin Syndrome	Hennekam Lymphangiectasia-Lymphedema Syndrome 1
Craniorhiny	Histiocytosis-Lymphadenopathy Plus Syndrome
Crouzon Syndrome	H Syndrome, Rosai-Dorfman Disease, Familial Hydronephrosis Congenital, With Cleft Palate, Characteristic Facies, Hypotonia, Mental Retardation
Curry-Jones Syndrome	Hypertrichosis lanuginosa; congenital; with/ without gingival hyperplasia; Ambras

Hypomelanosis of Ito	**Neurodevelopmental Disorder With Progressive Microcephaly, Spasticity, And Brain Anomalies**
Intellectual developmental disorder with cardiac defects and dysmorphic facies	**Nevoid Hypertrichosis**
Imagawa-Matsumoto Syndrome	**Oliver-Mcfarlane Syndrome**
Immunodeficiency 49	**Perching Syndrome**
Joubert Syndrome 10	**Polythelia Pilosa**
Kabuki Syndrome 2	**Pontocerebellar Hypoplasia Type 8**
Leigh Syndrome	**Porphyria Cutanea Tarda I, Ii** **Porphyria, Congenital Erythropoietic** **Variegate Porphyria**
Lethal Short-Limb Skeletal Dysplasia, Al Gazali Type	**Primary Multifocal Localized Hypertrichosis**
Leukodystrophy, Hypomyelinating, 17	**Ramon Syndrome**
Liang-Wang Syndrome	**Rubinstein-Taybi Syndrome I, Ii**
Lichtenstein Syndrome	**Sandestig-Stefanova Syndrome**
Light Fixation Seizure Syndrome	**Schinzel-Giedion Midface Retraction Syndrome**
Lipodystrophy, Congenital Generalized, Type 2 **Berardinelli-Seip Syndrome**	**Schwartz-Jampel Syndrome, Type 1**
Lissencephaly 7 With Cerebellar Hypoplasia **Lymphedema-Hypoparathyroidism Syndrome**	**Seckel Syndrome 9** **Segmental Odontomaxillary Dysplasia**
Mandibulofacial Dysostosis With Macroblepharon And Macrostomia	**Sialuria**
Mannosidosis, Alpha B, Lysosomal	**Spastic Paraplegia 53, Autossomal Recessive**
Marshall-Smith Syndrome	**Specific Granule Deficiency 2**
Meester-loeys syndrome **Melanocytic Nevus Syndrome**	**Spinocerebellar Ataxia, Autosomal Recessive 20** **Spinocerebellar Ataxia 42, Early-Onset, Severe, With Neurodevelopmental Deficits**
Mental Retardation, Autosomal Dominant 57 **Mental Retardation, Autosomal Recessive 35**	**Spondyloepimetaphyseal Dysplasia, Genevieve Type** **Stocco Dos Santos X-Linked Mental Retardation Syndrome**
Mental Retardation, Microcephaly, Epilepsy, And Coarse Face	**Sweeney-Cox Syndrome**
Mental Retardation, X-Linked 99, Syndromic, Female-Restricted	**Tenorio Syndrome**
Mental Retardation, X-Linked, Syndromic, Chudley-Schwartz Type	**Trichohepatoneurodevelopmental Syndrome**
Mental Retardation, X-Linked, Syndromic, Nascimento Type	**Trichomegaly**
Michelin Tire Baby Syndrome	**Vissers-Bodmer Syndrome**
Mitochondrial Complex I Deficiency, Nuclear Type 23	**Warburg Micro Syndrome**
Mucopolysaccharidosis, Type Ii, Iiic, Iiid, Vii	**Wiedemann-Steiner Syndrome**
Mullerian Derivatives, Persistence Of, With Lymphangiectasia And Postaxial Polydactyly **Multicentric Osteolysis, Nodulosis, And Arthropathy**	**Zimmermann-Laband Syndrome 1**

Table 1. Clinical features of hypertrichosis associated genetic syndromes.

Feature	Syndromes n (%)
Head and neck	97 (80.16)
Skeletal	95 (78.51)
Nervous system	89 (73.55)
Intellectual disability	63 (52.06)
Autosomal recessive	54 (44.62)
Abdominal	52 (42.97)
Genitourinary	48 (39.66)
Autosomal dominant	44 (36.36)
Cardiovascular	39 (32.23)
Dental anomalies	39 (32.23)
Respiratory	31 (25.61)
Other or unknown inheritance pattern*	25 (20.66)
Early death (until childhood)	22 (18.18)
Endocrine	17 (14.04)
Neoplasia	10 (8.26)

* X-linked, Y-linked, somatic mosaicism, somatic mutation, isolated cases.

Table 2. Genetic disturbs with hypertrichosis associated with neoplasia.

Syndrome	OMIM	Inheritance	Gene	Chromosomal
Beckwith-Wiedemann	**130650**	**AD**	***H19; ICR1;***	**11p15.5**
			KCNQ10T1;	
			CDKN1C	**11p15.4**
Bloom	**210900**	**AR**	***RECQL3***	**15q26.1**
Bohring-Opitz	**605039**	**AD**	***ASXL1***	**20q11.21**
Curry-Jones	**611707**	**Somatic mosaicism**	***SMO***	**7q32.1**
Donohue	**246200**	**AR**	***INSR***	**19p13.2**
Melanocytic nevus	**137550**	**Somatic mutation**	***NRAS***	**1p13.2**
Polythelia pilosa	**-**	**-**	**-**	**-**
Porphyria				
Cutanea tarda I, II	**176090** **176100**	**AD – AR**	***UROD***	**1p34.1**
Congenital erythropoietic porphyria	**263700**	**AR**	***UROS***	**10q26.2**
Variegate porphyria	**176200**	**AD**	***PPOX***	**1q23.3**
Rubinstein-Taybi I, II	**180849**	**AD**	***CREBBP***	**16p13.3**
	613684	**AD**	***EP300***	**22q13.2**
Schinzel-Giedion midface retraction syndrome	**269150**	**AD**	***SETBP1***	**18q12.3**

AD: autosomal dominant; AR: autosomal recessive; OMIM: Online Mendelian Inheritance in Man.

4.1.2 Artigo Científico 2

Dental anomalies in syndromes displaying hypertrichosis in the clinical spectrum

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Abstract

Hypertrichosis and dental anomalies may occur alone or in combination in the spectrum of many syndromes. To identify genetic entities characterized by hypertrichosis and dental anomalies, a search was performed in the Online Mendelian Inheritance in Man with the terms "*hypertrichosis*" or "*hirsutism*" and "tooth". Non-dependent androgen metabolism disturbances were classified as hypertrichosis. Genetic entities with hypertrichosis and dental anomalies were included in the study. Additional search was performed in PubMed and Orphanet databases when necessary, to complement for scientific articles. An integrative analysis with the genes associated with the identified syndromes was conducted with STRING to characterize biological processes, pathways and interactive networks. The p-values were subjected to the false discovery rate for correction of multiple tests. Thirty-nine syndromes were identified, and dental agenesis was the most frequent dental anomaly, present in 41.02% (n=16) of the syndromes. Causative genes were identified in 33 out of 39 genetic syndromes. Among them, 39 genes were identified and 38 were analyzed by STRING, which showed 148 biological processes and 3 pathways statistically significant. The most significant biological processes were disassembly of the nucleosome (GO: 0006337, p=1.09e-06), chromosomal organization (GO: 0051276, p=1.09e-06) and remodeling of the chromatin (GO: 0006338, p=7.86e-06), and the pathways were hepatocellular carcinoma (hsa05225, p=5.77e-05), thermogenesis (hsa04714, p=0.00019) and cell cycle (hsa04110, p=0.0433). The study shows that the identification of hypertrichosis and dental anomalies may raise the suspicion of a genetic condition and highlights its main biological process and pathways.

Keywords: Hypertrichosis; Genetic Disease; Inborn Genetic Disease; Abnormalities, Teeth; Abnormalities, Tooth.

Introduction

Hypertrichosis is characterized by an abnormal increase of hair anywhere on the body and independent of androgens. It can be result from the use of drugs, hereditary factors or metabolic disorders, and occur of isolated form or associated with other clinical manifestations constituting a syndrome. The isolated form is infrequent, with an unknown incidence, but its frequency is increased when participates as a phenotype of syndromes [1].

Although important genetic features can be found in the syndromic forms, which provide data for the definition of the phenotype [2], clinical descriptions are useful for patient care, especially in the complex cases. A common clinical manifestation associated to hypertrichosis is dental anomalies. The latter refers to variations in color, eruption, number, size and form of the teeth, and its occurrence varies based on the type of anomaly, dentition and population. Dental anomalies are relevant clinical signs and can provide important clues for the suspicion of a genetic entity and for the differential diagnosis of the syndromes with hypertrichosis [3]. The goal of this study was to identify the set of genetic syndromes with dental anomalies coinciding with the clinical presence of hypertrichosis.

Material and methods

A search was performed from June 2020 to October 2020 in the electronic database Online Mendelian Inheritance in Man (OMIM, https://www.omim.org) with the associations of the terms "*hypertrichosis*" or "*hirsutism*" and “tooth”. Non-dependent androgen metabolism disturbances were classified as hypertrichosis. The phenotypic and genotypic manifestations were predominantly collected at OMIM by one collaborator, and, when necessary, an additional search was performed in the electronic database PubMed (https://pubmed.ncbi.nlm.nih.gov) and Orphanet (https://www.orpha.net/consor/cgi-bin/index.php) to complement the search for scientific articles.Dental anomalies were grouped according to the classification established by De La Dure-Molla et al (2019). STRING, protein-protein interaction networks functional enrichment analysis (http:/string-db.org), was used to investigate

the biological processes, pathways and interaction network. Thep values were subjected to false discovery rate to correct multiple tests, and values ≤0.05 were considered significant.

Results

Seventy-seven entries were identified, however 39 syndromes containing hypertrichosis and dental anomalies in the clinical spectrum were included in the study (Table 1). Entries with description of genes or related to hirsutism were excluded, however overlapping syndromes were also included. Only segmental odontomaxillary dysplasia wasn't found in OMIM, but found in scientific articles in Pubmed.

The frequency of dental anomalies are listed in Table 2. Dental agenesis was the most frequent dental anomaly in this study, present in 41.02% (n=16) of the syndromes. Other common anomalies included delayed tooth eruption 35.89% (n=14), widely spaced teeth 28.20% (n=11), dental malocclusion 25.64% (n=10) and tooth shape change 25.64% each (n=10).

Among identified syndromes, 15 (38.46%) are inherited as an autosomal recessive trait, whereas 15 (38.46%) are autosomal dominant. Isolated cases (n=4), X-linked dominant inheritance (n=4), X-linked recessive inheritance (n=2) and mosaic (n=1) were also identified. Causative genes are recognized in thirty-three of thirty-nine syndromes. Among them, 39 genes were recognized, nevertheless a genetic entity can be linked to more than one gene, and some entities are not related to any gene until nowadays. STRING analyses were performed with 38 genes, because one gene was not recognized by the software (*RFF125*), and it showed 148 biological processes and 3 pathways. Figure 1 shows the protein-protein interactions network. The most significant biological processes were nucleosome disassembly (GO:0006337, P=1.09e-06), chromosome organization (GO:0051276, P=1.09e-06) and chromatin remodeling (GO:0006338, P=7.86e-06), and the pathways were hepatocellular carcinoma (hsa05225, P=5.77e-05), thermogenesis (hsa04714, P= 0.00019) and cell cycle (hsa04110, P=0.0433) (Supplementary Table 1 and 2).

Discussion

In the current research, 39 syndromes with dental anomalies associated to hypertrichosis were identified, together with other important clinical features. Despite differences in the final structures and functions, this association is possible because ectodermal organs, as the hair and teeth, originate from the epithelium and the mesenchyme. The mesenchyme typically provides the first instructive signal, which is followed by the development of an early signaling node, the epithelial placode [4].Morphogenesis is supported by placode buds into or out of the mesenchyme, and subsequent proliferation, cell movements, and epithelium and mesenchyme differentiation [4]. Thus, countless genes can participate in these processes.

This highlights the degree to which common molecular mechanisms regulate many aspects of the early development of hair and teeth. In this study, were found 7 genes in BMP, 6 in FGF, 7 in Shh and 18 in Wnt pathways. Besides that, there are significant differences between the hair and teeth, especially in the spatial and temporal dynamics of placode growth, suggesting that in different contexts, there may be specific means of modulating the signaling pathways and of the 39 genes found, 16 not participate of the four main pathways. It is likely that the deregulation of these pathways (BMP, FGF, Shh and Wnt) is responsible for the occurrence of hypertrichosis and dental anomalies.

Extensive genetic studies of defective mouse mutants have shown that signaling pathways (BMP, FGF, Shh, and Wnt) are used reiteratively in many stages of the production of various skin appendages and of teeth, in biological processes through pathways such as cell cycle. [5] The Wnt pathway plays an essential role during hair follicle induction and also in the dental one. Shh is related to morphogenesis and differentiation at an advanced stage, while BMP is related to cell differentiation [5].

The lymphoid augmentation factor 1 (Lef-1) is necessary for the development of multiple organ systems, including the development of hair and teeth and its role in Wnt signaling has been established. The expression of Lef-1 regulates the signaling of Wnt and target genes of Wnt, as well as mechanisms of cell proliferation, while miR-26b reduced the levels of expression of the target gene of Wnt [6].Lef-1 is regulated by FGF signaling and the overexpression of Lef-1 in cells results in increased epithelial invagination and formation of extra hair follicles. Lef-1 deficiency results in dental morphogenesis stuck in the late phase of the button, and Lef-1 is only needed temporarily in the dental epithelium for tooth development [6]. At the molecular level,

Lef-1 is necessary to induce an expression of FGF4, which regulates an expression of FGF3 and Shh in the tooth germ [6].

Shh is critical for dental epithelial cells during tooth development and inhibition of Shh signaling results in apoptosis located in the dental epithelium [7]. Hence, in both, disruption of individual signaling pathways also causes related developmental defects. Shh also promote cell proliferation in anagen hair follicles [5].

The antagonistic interactions between FGF and Bmp in the oral epithelium play an important role in the positioning of the tooth formation sites. These FGF-BMP interactions control the expression of *Bmp4, Pax9, Barx1, Msx1, Msx2, Dlx* and other genes in the mesenchyme, whose combinatorial expression influences the type, number, size and shape of the tooth [5]. During the beginning of dental formation, the BMP signaling in the epithelium antagonizes the FGFpathways, and this interaction is designed to determine the locations of dental formation. The interruption of BMP activity due to the excessive expression of noggin blocks the molar development and the differentiation of epithelial cells in the final stage [8]. BMP signaling has an inhibitory role in hair follicle induction and morphogenesis, which needs to be antagonized mainly by noggin to facilitate placebo induction. Overexpression of noggin in the epidermis resulted in thickening of the epidermis, increased hair density and alteration of hair types [8].

Using ontology analysis, were found 148 biologic processes and the pathways of hepatocellular carcinoma, thermogenesis and cell cycle, formed by genes that interact with each other constituting a large network. In most cases, dental agenesis is caused by mutations that interrupt epithelial Wnt/β-catenin signaling. [9] It is one of the fundamental signaling pathways for the growth and development of the hair follicle and tooth, but it is also responsible for contributing to the development of hepatocellular carcinoma and hepatoblastoma [10,11]. It is suggested that mutations in the genes found in the present study may interfere with the Wnt/β-catenin pathway.

The activation or under-activation of signaling pathways, such as shh, notch, TFG, BMP and Wnt/β-catenin plays a key role in hair cycle [5,8]. This knowledge helps understanding the molecular basis of disturbances and identifying intracellular targets for the development of therapies, such as hair loss treatment [10].

Together, our results highlight that the identification of hypertrichosis and dental anomalies should raise the suspicion of the possibility of a genetic syndrome by the

health professional for the proper management and care of the patient. Dental anomalies are frequent changes in genetic syndromes and can cause aesthetic and functional disorders leading the patient to seek dental treatment. Patients with these syndromes may experience difficulty in accessing the qualified health system, and there may be delays in diagnosis. Treatment and follow-up must be interdisciplinary, including the presence of the dental surgeon to assess patients' dental needs. Thus, the dental evaluation can be a gateway for the diagnosis and management of patients with genetic diseases with dental involvement and clinical presence of hypertrichosis. The main dental anomalies described in individuals with genetic alterations associated with the clinical presence of hypertrichosis were: agenesis, delayed tooth eruption and widely spaced teeth. Further studies are needed to better understand these associations.

Figure 1. Protein-protein interaction network

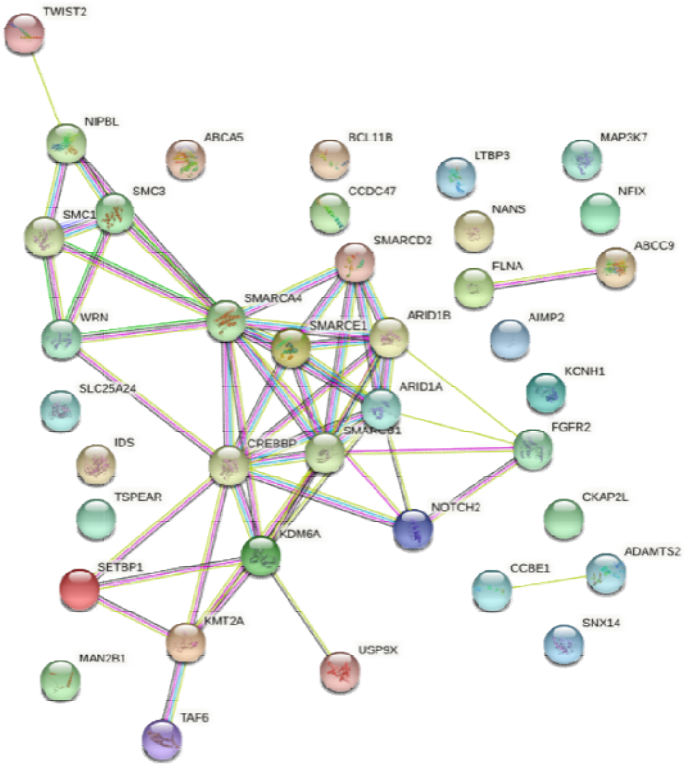

Figure 1. Protein-protein interaction network with the genes associated with syndromes with hypertrichosis and dental anomalies. Nineteen out of 38 genes formed a node including *ARID1A*, *ARID1B*, *CREBBP*, *FGFR2*, *KDM6A*, *KMT2A*, *NIPBL*, *NOTCH2*, *SETBP1*, *SMARCA4*, *SMARCB1*, *SMARCD2*, *SMARCE1*, *SMC1A*, *SMC3*, *TAF6*, *TWIST2*, *USP9X*, and *WRN* (p<1.0e-16). Different colors represent different levels of evidence of connection between proteins. Light blue represents curated databases, purple experimental evidence, green gene neighborhood, red gene fusions, blue gene co-occurrence, light green evidence from text mining, black co-expression, and violet protein homology. This analysis had an average confidence score of 0.472, suggesting a low rate for false-positive interactions.

Table 1. Syndromes with hypertrichosis and dental anomalies.

Syndrome	OMIM	Inheritance	Gene	Chromosomal	Dental Anomalies	Reference
Alazami-Yuan syndrome	#617126	AR	*TAF6*	7q22.1	Crowded teeth	12
Barber-Say syndrome	#209885	AD	*TWIST2*	2q37.3	Taurodontism in the molar tooth, early apical closure in permanent and incisive blade-shaped anterior teeth, delayed tooth eruption, infra-occluded molars and wide alveolar grooves	13
Bloom syndrome	#210900	AR	*RECQL3* (*WRN*)	15q26.1	Agenesis of the upper lateral incisors	14
Cantu syndrome	#239850	AD	*ABCC9*	12p12.1	Dental malocclusion	15
Chromosome 17q21.31 duplication syndrome	#613533	IC	-	17q21.31	Crowded incisor	16
Coffin-siris syndrome	#135900	AD	*ARID1B,*	6q25.3	Abnormal dental shape and hypodontia	17
	#614607		*ARID1A, SMARCB1, SMARCA4, SMARCE1*	1p36.11		
	#614608			22q11.23		
	#614609			19p13.2		
	#616938			17q21.2		
Cornelia de Lange syndrome	#122470	AD	*NIPBL,*	5p13.2	Agenesis of the lower lateral incisors, agenesis of deciduous second molars, deciduous macrodontic teeth, permanent macrodontic teeth, agenesis of the lower deciduous lateral incisors, conoid incisor, delayed tooth eruption, microdontia, dysmorphic teeth and widely spaced and rotated teeth	18
	#610759		*SMC3*	10q25.2		

Crouzon syndrome	**#123500**	**AD**	***FGFR2***	**10q26.13**	**Agenesis of deciduous second molars and dental crowding**	**19**
Dental anomalies and short stature	**#601216**	**AR**	***LTBP3***	**11q13.1**	**Enamel hypoplasia, widely spaced teeth, retention of deciduous teeth, delayed eruption of permanent teeth, imperfect amelogenesis, taurodontic pulp chambers, microdontic primary teeth, permanent tooth oligodontics and enamel discoloration**	**20**
Developmental and epileptic encephalopathy 85 with or without midline brain defects	**#301044**	**XLD**	***SMC1A***	**Xp11.22**	**Crowded teeth, single central incisor**	**21**
Ectodermal dysplasia 14, hair/tooth type with or without hypohidrosis	**#618180**	**AR**	***TSPEAR***	**21q22.3**	**Oligodontics, conoid teeth**	**22**
Ehlers-Danlos syndrome	**#225410**	**AR**	***ADAMTS2***	**5q35.3**	**Upper canine agenesis, lower premolar agenesis, lower molar agenesis, lower incisor agenesis and lower premolar agenesis, permanent teeth with color change, microdontia, malocclusion**	**23**
Fillippi syndrome	**#272440**	**AR**	***CKAP2L***	**2q14**	**Microdontia, hypodontia (rare), saw teeth, widely spaced teeth**	**24**
Fontaine Progeroid syndrome	**#612289**	**AD**	***SLC25A24***	**1p13.3**	**Hypodontia, microdontia, oligodontia and widely spaced teeth, bell-shaped crown, spindle-shaped roots and small or absent pulp chamber**	**25**
Frontometaphyseal dysplasia	**#305620** **#617137**	**XLR** **AD**	***FLNA*** ***MAP3K7***	**Xq28** **6q15**	**Selective tooth agenesis, delayed tooth eruption, retained deciduous teeth, malocclusion, irregularly implanted teeth.**	**26**
Hypertrichosis, congenital generalized **Hypertrichosis, congenital generalized, with or without gingival hyperplasia**	**#307150** **#135400**	**XLD** **AR**	**-** ***ABCA5***	**Xq27.1** **17q24.2-q24.3**	**Delay in tooth eruption, hypodontia, and dental shape alteration** **Widely spaced teeth, delayed tooth eruption**	**27**
Hypomelanosis of Ito	**#300337**	**Somatic Mosaic**	**-**	**Xp11**	**Upper incisors with claw-shaped cusps and anterior deciduous teeth with yellowish-brown crowns and widely spaced teeth**	**28**
Hajdu-Cheney syndrome	**#102500**	**AD**	***NOTCH2***	**1p12**	**Early tooth loss and malocclusion**	**29**

Hennekan Lymphangiectasia-Syndrome 1	**#235510**	**AR**	***CCBE1***	**18q21.32**	**Oligodontia, peg-shaped incisors and delayed eruption**	**30**
Immunodeficiency 49	**#617237**	**AD**	***BCL11B***	**14q32.2**	**Neonatal teeth**	**31**
Kabuki syndrome 2	**#300867**	**XLD**	***KDM6A***	**Xp11.3**	**Macrodontics, dental malocclusion, agenesis of upper lateral incisors and inner central incisors, neonatal teeth (rare)**	**32**
Hypomyelinating leukodystrophy-17	**#618006**	**AR**	***AIMP2***	**7p22.1**	**Widely spaced teeth**	**33**
Lichtenstein syndrome	**#246550**	**IC**	**-**	**-**	**Enamel hypoplasia and discolored teeth**	**34**
Mandibulofacial dysostosis with macroblepharon and macrostomia	**#602562**	**IC**	**-**	**-**	**Ectopic teeth and oligodontics**	**35**
Mannosidosis, alpha B, lysosomal	**#248500**	**AR**	***MAN2B1***	**19p13.13**	**Teeth widely spaced**	**36**
Marshall-Smith Syndrome	**#602535**	**AD**	***NFIX***	**19p13.13**	**Dental malocclusion**	**37**
Mental retardation, X-linked 99, syndromic, female-restricted	**#300968**	**XLD**	***USP9x***	**Xp11.4**	**Widely spaced teeth, malocclusion, crowding, tooth agglomeration**	**38**
Mucopolysaccharidosis, type II	**#309900**	**XLR**	***IDS***	**Xq28**	**Delay in tooth eruption and widely spaced teeth**	**39**
Ramon syndrome	**#266270**	**AR**	**-**	**-**	**Delay in tooth eruption**	**40**
Rubinstein-Taybi syndrome	**#180849**	**AD**	***CREBBP***	**16p13.3**	**Dental crowding, upper incisors with claw-shaped cusps, malocclusion, wedge-shaped or screwdriver and enamel discoloration**	**41**
Segmental Odontomaxillary Dysplasia	**-**	**IC**	**-**	**-**	**Pre-molar agenesis and delayed eruption of permanent molars**	**42**
Schinzel-Giedion syndrome	**#269150**	**AD**	***SETBP1***	**18q12.3**	**Macrodontics, tooth eruption delays, agenesis of the upper deciduous lateral incisors and agenesis of the lower deciduous lateral incisors**	**43**
Specific granule deficiency 2	**#617475**	**AR**	***SMARCD2***	**17q23.3**	**Irregularly shaped teeth, misaligned teeth and incomplete amelogenesis**	**44**
Spinocerebellar ataxia, autosomal recessive 20	**#616354**	**AR**	***SNX14***	**6q14.3**	**Delay in tooth eruption and crowding**	**45**
Spondyloepimetaphyseal dysplasia,	**#610442**	**AR**	***NANS***	**9q22.33**	**Dental misalignment**	**46**

Camera-Genevieve type						
Trichhepatoneurodevopmental Syndrome	**#618268**	**AR**	***CCDC47***	**17q23.3**	**Widely spaced teeth, dental crowding, microdontia, dental malocclusion**	**47**
Tenorio syndrome	**#616260**	**AD**	***RFF125***	**18q12.1**	**Delay in tooth eruption**	**48**
Weidemann-Steinner syndrome	**#605130**	**AD**	***KMT2A***	**11q23.3**	**Delay in tooth eruption, supernumerary tooth between central incisor and deciduous canine, malocclusion, hypodontia and ectopic teeth**	**49**
Zimmermann-Laband syndrome	**#135500**	**AD**	***KCNH1***	**1q32.2**	**Delay in dental eruption**	**50**

AD: autosomal dominant; AR: autosomal recessive; OMIM: Online Mendelian Inheritance in Man; XLD: x-linked dominant; XLR: x-linked recessive; IC: isolated cases.

Table 2. Frequency of the dental anomalies in syndromes hypertrichosis.

Dental anomalies	n (%)	Anomaly description*
Dental agenesis	16 (41.02)	The absence of one or more teeth of the normal series due to a failure in development. The absence of five or less teeth is called hypodontia and the absence of six or more teeth is called oligodontia
Delay in tooth eruption	14 (35.89)	Apparent absence of one or more teeth during visual inspection of the oral cavity. The physiological sequential eruption related to age should be taken into account during assessments
Widely spaced teeth	11 (28.20)	Separation of teeth from the same dental arch by spaces larger than normal. It differs from the diastema, which is the increase in space between two adjacent teeth
Dental malocclusion	10 (25.64)	Alteration of dental arch relationships in shape or position
Tooth shape change	10 (25.64)	It can be presented in several ways. In the present study, changes in the tooth shape described were: saw tooth, wedge-shaped tooth, bell-shaped crown, conoid teeth, claw-shaped cusps, shovel-shaped tooth
Dental crowding	9 (23.07)	Changes in tooth alignment in the dental arch
Tooth malposition	7 (17.94)	Location of a tooth out of its normal position or orientation
Microdontics	6 (15.38)	Mesiodistal tooth diameter more than 2 SD below average
Macrodontics	4 (10.25)	Diameter (width) of the mesiodistal tooth more than 2 SD above average
Tooth color anomaly	3 (7.69)	A tooth can have a variety of abnormal colors, such as yellow, brown, or discolored teeth
Neonatal Tooth	2 (5.12)	Eruption of teeth at or immediately after birth
Taurodontism	2 (5.12)	Elongated pulp chambers and apical displacement of the bifurcation or root trifurcation

*Description according to De La Dure-Molla *et al.* (2019)

Supplementary Table 1. Biological processes characterized with the list of altered genes in syndromes with hypertrichosis and dental anomalies.

	Term description	Observed gene count	Background gene count	False discovery rate	Matching proteins in your network
GO:0006337	nucleosome disassembly	5	18	1.09e-06	*SMARCB1, ARID1A, SMARCE1, SMARCD2, SMARCA4*
GO:0051276	chromosome organization	14	999	1.09e-06	*CREBBP, SMARCB1, NIPBL, WRN, ARID1A, SMC1A, SMARCE1, ARID1B, SMC3, MAP3K7, KDM6A, SMARCD2, SMARCA4, KMT2A*
GO:0006338	chromatin remodeling	7	156	7.86e-06	*SMARCB1, ARID1A, SMARCE1, ARID1B, KDM6A, SMARCD2, SMARCA4*
GO:0006325	chromatin organization	10	683	0.00015	*CREBBP, SMARCB1, ARID1A, SMARCE1, ARID1B, MAP3K7, KDM6A, SMARCD2, SMARCA4, KMT2A*
GO:0010604	positive regulation of macromolecule metabolic process	19	3081	0.00020	*AIMP2, NOTCH2, CREBBP, SMARCB1, NIPBL, WRN, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, MAP3K7, KDM6A, NFIX, SMARCD2, SMARCA4, CCBE1, FGFR2, KMT2A*
GO:0019219	regulation of nucleobase-containing compound metabolic process	22	4133	0.00020	*NOTCH2, CREBBP, SMARCB1, SETBP1, NIPBL, WRN, USP9X, ARID1A, SMC1A, SMARCE1, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, TAF6, FGFR2, KMT2A, TWIST2*
GO:0045934	negative regulation of nucleobase-containing compound metabolic process	13	1424	0.00028	*CREBBP, NIPBL, USP9X, ARID1A, SMC1A, SMARCE1, SMC3, FLNA, NFIX, SMARCA4, FGFR2, KMT2A, TWIST2*
GO:0045935	positive regulation of nucleobase-containing compound metabolic process	14	1770	0.00040	*CREBBP, SMARCB1, NIPBL, WRN, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, NFIX, SMARCD2, SMARCA4, FGFR2, KMT2A*
GO:0051173	positive regulation of nitrogen compound metabolic process	18	2946	0.00040	*AIMP2, NOTCH2, CREBBP, SMARCB1, NIPBL, WRN, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, MAP3K7, NFIX, SMARCD2, SMARCA4, CCBE1, FGFR2, KMT2A*
GO:2000112	regulation of cellular macromolecule biosynthetic process	21	4050	0.00040	*NOTCH2, CREBBP, SMARCB1, SETBP1, NIPBL, USP9X, ARID1A, SMC1A, SMARCE1, ARID1B, BCL11B, SMC3, MAP3K7, FLNA,*

					NFIX, SMARCD2, SMARCA4, TAF6, FGFR2, KMT2A, TWIST2
GO:0019827	stem cell population maintenance	5	118	0.00044	*NOTCH2, NIPBL, ARID1A, SMC1A, SMC3*
GO:0031325	positive regulation of cellular metabolic process	18	3060	0.00045	*AIMP2, NOTCH2, CREBBP, SMARCB1, NIPBL, WRN, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, MAP3K7, NFIX, SMARCD2, SMARCA4, CCBE1, FGFR2, KMT2A*
GO:0032984	protein-containing complex disassembly	6	220	0.00045	*SMARCB1, SNX14, ARID1A, SMARCE1, SMARCD2, SMARCA4*
GO:2000113	negative regulation of cellular macromolecule biosynthetic process	12	1348	0.00050	*CREBBP, NIPBL, USP9X, ARID1A, SMC1A, SMARCE1, SMC3, FLNA, NFIX, SMARCA4, FGFR2, TWIST2*
GO:0044260	cellular macromolecule metabolic process	26	6413	0.00059	*AIMP2, CCDC47, NOTCH2, CREBBP, SMARCB1, KCNH1, NIPBL, WRN, USP9X, ARID1A, SMC1A, IDS, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, KDM6A, NFIX, SMARCD2, MAN2B1, SMARCA4, TAF6, FGFR2, KMT2A, TWIST2*
GO:0016043	cellular component organization	23	5163	0.00070	*AIMP2, CCDC47, ADAMTS2, CREBBP, SMARCB1, NIPBL, WRN, SNX14, USP9X, ARID1A, SMC1A, SMARCE1, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, KDM6A, ABCA5, SMARCD2, SMARCA4, FGFR2, KMT2A*
GO:0032501	multicellular organismal process	26	6507	0.00070	*AIMP2, CCDC47, ADAMTS2, NOTCH2, CREBBP, SMARCB1, KCNH1, NIPBL, WRN, LTBP3, USP9X, ARID1A, TSPEAR, SMC1A, SMARCE1, ARID1B, BCL11B, SMC3, FLNA, KDM6A, ABCA5, SMARCA4, CCBE1, FGFR2, KMT2A, TWIST2*
GO:0060255	regulation of macromolecule metabolic process	25	6072	0.00070	*AIMP2, NOTCH2, CREBBP, SMARCB1, SETBP1, NIPBL, WRN, USP9X, ARID1A, SMC1A, SMARCE1, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, KDM6A, NFIX, SMARCD2, SMARCA4, TAF6, CCBE1, FGFR2, KMT2A, TWIST2*
GO:0006355	regulation of transcription, DNA-templated	19	3661	0.00079	*NOTCH2, CREBBP, SMARCB1, SETBP1, NIPBL, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, TAF6, FGFR2, KMT2A, TWIST2*
GO:0010468	regulation of gene expression.	21	4533	0.00093	*NOTCH2, CREBBP, SMARCB1, SETBP1, NIPBL, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, MAP3K7, FLNA, KDM6A, NFIX, SMARCD2, SMARCA4, TAF6, CCBE1, FGFR2, KMT2A, TWIST2*
GO:0032502	developmental process	23	5401	0.00093	*AIMP2, CCDC47, ADAMTS2, NOTCH2, CREBBP, SMARCB1, KCNH1, NIPBL, WRN, USP9X, ARID1A, SMC1A, SMARCE1, ARID1B, BCL11B, SMC3, FLNA, KDM6A, SMARCA4, CCBE1,*

					FGFR2, KMT2A, TWIST2
GO:0034654	nucleobase-containing compound biosynthetic process	17	3031	0.00093	*NANS, NOTCH2, CREBBP, SMARCB1, NIPBL, WRN, ARID1A, ARID1B, BCL11B, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, TAF6, KMT2A, TWIST2*
GO:0051171	regulation of nitrogen compound metabolic process	24	5827	0.00093	*AIMP2, NOTCH2, CREBBP, SMARCB1, SETBP1, NIPBL, WRN, USP9X, ARID1A, SMC1A, SMARCE1, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, TAF6, CCBE1, FGFR2, KMT2A, TWIST2*
GO:1903508	positive regulation of nucleic acid-templated transcription	12	1520	0.00093	*CREBBP, SMARCB1, NIPBL, ARID1A, SMARCE1, ARID1B, BCL11B, NFIX, SMARCD2, SMARCA4, FGFR2, KMT2A*
GO:0006996	organelle organization	17	3131	0.0010	*CCDC47, CREBBP, SMARCB1, NIPBL, WRN, USP9X, ARID1A, SMC1A, SMARCE1, ARID1B, SMC3, MAP3K7, FLNA, KDM6A, SMARCD2, SMARCA4, KMT2A*
GO:0048518	positive regulation of biological process	23	5459	0.0010	*AIMP2, NOTCH2, CREBBP, SMARCB1, NIPBL, WRN, LTBP3, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, KDM6A, NFIX, SMARCD2, SMARCA4, CCBE1, FGFR2, KMT2A, TWIST2*
GO:0009791	post-embryonic development	4	90	0.0011	*CCDC47, BCL11B, FGFR2, KMT2A*
GO:0044271	cellular nitrogen compound biosynthetic process	18	3528	0.0011	*NANS, AIMP2, NOTCH2, CREBBP, SMARCB1, NIPBL, WRN, ARID1A, ARID1B, BCL11B, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, TAF6, KMT2A, TWIST2*
GO:0080090	regulation of primary metabolic process	24	5982	0.0011	*AIMP2, NOTCH2, CREBBP, SMARCB1, SETBP1, NIPBL, WRN, USP9X, ARID1A, SMC1A, SMARCE1, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, TAF6, CCBE1, FGFR2, KMT2A, TWIST2*
GO:0043170	macromolecule metabolic process	27	7453	0.0012	*AIMP2, CCDC47, ADAMTS2, NOTCH2, CREBBP, SMARCB1, KCNH1, NIPBL, WRN, USP9X, ARID1A, SMC1A, IDS, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, KDM6A, NFIX, SMARCD2, MAN2B1, SMARCA4, TAF6, FGFR2, KMT2A, TWIST2*
GO:0090304	nucleic acid metabolic process	19	3941	0.0012	*AIMP2, NOTCH2, CREBBP, SMARCB1, NIPBL, WRN, ARID1A, SMC1A, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, TAF6, KMT2A, TWIST2*
GO:1902661	positive regulation of glucose mediated signaling pathway	2	3	0.0012	*SMARCB1, SMARCA4*

GO:0006351	transcription, DNA-templated	15	2569	0.0013	*NOTCH2, CREBBP, SMARCB1, NIPBL, ARID1A, ARID1B, BCL11B, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, TAF6, KMT2A, TWIST2*
GO:0006356	regulation of transcription by RNA polymerase I	3	32	0.0013	*SMARCB1, FLNA, SMARCA4*
GO:0010605	negative regulation of macromolecule metabolic process	15	2558	0.0013	*NOTCH2, CREBBP, SMARCB1, NIPBL, USP9X, ARID1A, SMC1A, SMARCE1, SMC3, FLNA, NFIX, SMARCA4, FGFR2, KMT2A, TWIST2*
GO:0031323	regulation of cellular metabolic process	24	6082	0.0013	*AIMP2, NOTCH2, CREBBP, SMARCB1, SETBP1, NIPBL, WRN, USP9X, ARID1A, SMC1A, SMARCE1, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, TAF6, CCBE1, FGFR2, KMT2A, TWIST2*
GO:0006352	DNA-templated transcription, initiation	5	213	0.0015	*NOTCH2, CREBBP, SMARCB1, SMARCA4, TAF6*
GO:0045892	negative regulation of transcription, DNA-templated	10	1169	0.0015	*CREBBP, NIPBL, USP9X, ARID1A, SMARCE1, FLNA, NFIX, SMARCA4, FGFR2, TWIST2*
GO:0051172	negative regulation of nitrogen compound metabolic process	14	2307	0.0016	*CREBBP, SMARCB1, NIPBL, USP9X, ARID1A, SMC1A, SMARCE1, SMC3, FLNA, NFIX, SMARCA4, FGFR2, KMT2A, TWIST2*
GO:0048522	positive regulation of cellular process	21	4898	0.0017	*AIMP2, NOTCH2, CREBBP, SMARCB1, NIPBL, WRN, LTBP3, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, CCBE1, FGFR2, KMT2A, TWIST2*
GO:0007062	sister chromatid cohesion	3	39	0.0018	*NIPBL, SMC1A, SMC3*
GO:0032876	negative regulation of DNA endoreduplication	2	5	0.0018	*SMC1A, SMC3*
GO:0006139	nucleobase-containing compound metabolic process	20	4551	0.0019	*NANS, AIMP2, NOTCH2, CREBBP, SMARCB1, NIPBL, WRN, ARID1A, SMC1A, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, TAF6, KMT2A, TWIST2*
GO:0006807	nitrogen compound metabolic process	28	8349	0.0024	*NANS, AIMP2, CCDC47, ADAMTS2, NOTCH2, CREBBP, SMARCB1, KCNH1, NIPBL, WRN, USP9X, ARID1A, SMC1A, IDS, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, KDM6A, NFIX, SMARCD2, MAN2B1, SMARCA4, TAF6, FGFR2, KMT2A, TWIST2*
GO:0010628	positive regulation of gene	12	1826	0.0025	*CREBBP, SMARCB1, NIPBL, ARID1A, ARID1B, BCL11B, KDM6A,*

	expression				*NFIX, SMARCA4, CCBE1, FGFR2, KMT2A*
GO:0031324	negative regulation of cellular metabolic process	14	2463	0.0026	*CREBBP, SMARCB1, NIPBL, USP9X, ARID1A, SMC1A, SMARCE1, SMC3, FLNA, NFIX, SMARCA4, FGFR2, KMT2A, TWIST2*
GO:0048856	anatomical structure development	21	5085	0.0026	*AIMP2, CCDC47, ADAMTS2, NOTCH2, CREBBP, SMARCB1, KCNH1, NIPBL, WRN, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, FLNA, KDM6A, SMARCA4, CCBE1, FGFR2, KMT2A, TWIST2*
GO:0034645	cellular macromolecule biosynthetic process	17	3518	0.0027	*AIMP2, NOTCH2, CREBBP, SMARCB1, NIPBL, WRN, ARID1A, ARID1B, BCL11B, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, TAF6, KMT2A, TWIST2*
GO:0040009	regulation of growth rate	2	7	0.0027	*NOTCH2, WRN*
GO:0007275	multicellular organism development	20	4726	0.0028	*AIMP2, CCDC47, ADAMTS2, NOTCH2, CREBBP, SMARCB1, NIPBL, WRN, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, FLNA, KDM6A, SMARCA4, CCBE1, FGFR2, KMT2A, TWIST2*
GO:0007399	nervous system development	13	2206	0.0031	*NOTCH2, SMARCB1, NIPBL, WRN, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, FLNA, KDM6A, SMARCA4, FGFR2*
GO:0001188	RNA polymerase I preinitiation complex assembly	2	9	0.0035	*SMARCB1, SMARCA4*
GO:0048096	chromatin-mediated maintenance of transcription	2	9	0.0035	*ARID1A, ARID1B*
GO:0048523	negative regulation of cellular process	19	4454	0.0039	*AIMP2, NOTCH2, CREBBP, SMARCB1, NIPBL, USP9X, ARID1A, SMC1A, SMARCE1, BCL11B, SMC3, FLNA, ABCA5, NFIX, SMARCA4, TAF6, FGFR2, KMT2A, TWIST2*
GO:1901838	positive regulation of transcription of nucleolar large rRNA by RNA polymerase I	2	10	0.0041	*SMARCB1, SMARCA4*
GO:0010629	negative regulation of gene expression	11	1670	0.0042	*NOTCH2, CREBBP, NIPBL, USP9X, ARID1A, SMARCE1, FLNA, NFIX, SMARCA4, FGFR2, TWIST2*
GO:0006357	regulation of transcription by RNA polymerase II	14	2633	0.0044	*CREBBP, SMARCB1, SETBP1, NIPBL, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, NFIX, SMARCD2, SMARCA4, FGFR2, KMT2A*

GO:0010467	gene expression.	17	3733	0.0046	*AIMP2, ADAMTS2, NOTCH2, CREBBP, SMARCB1, NIPBL, ARID1A, ARID1B, BCL11B, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, TAF6, KMT2A, TWIST2*
GO:2000615	regulation of histone H3-K9 acetylation	2	11	0.0047	*SMARCB1, KMT2A*
GO:0030324	lung development	4	162	0.0048	*AIMP2, ADAMTS2, CCBE1, FGFR2*
GO:0044237	cellular metabolic process	28	8797	0.0050	*NANS, AIMP2, CCDC47, NOTCH2, CREBBP, SMARCB1, KCNH1, NIPBL, WRN, SNX14, USP9X, ARID1A, SMC1A, IDS, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, KDM6A, NFIX, SMARCD2, MAN2B1, SMARCA4, TAF6, FGFR2, KMT2A, TWIST2*
GO:0044238	primary metabolic process	28	8808	0.0050	*NANS, AIMP2, CCDC47, ADAMTS2, NOTCH2, CREBBP, SMARCB1, KCNH1, NIPBL, WRN, USP9X, ARID1A, SMC1A, IDS, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, KDM6A, NFIX, SMARCD2, MAN2B1, SMARCA4, TAF6, FGFR2, KMT2A, TWIST2*
GO:0044249	cellular biosynthetic process	19	4567	0.0050	*NANS, AIMP2, NOTCH2, CREBBP, SMARCB1, NIPBL, WRN, ARID1A, ARID1B, BCL11B, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, TAF6, FGFR2, KMT2A, TWIST2*
GO:0045893	positive regulation of transcription, DNA-templated	10	1435	0.0050	*CREBBP, SMARCB1, NIPBL, ARID1A, ARID1B, BCL11B, NFIX, SMARCA4, FGFR2, KMT2A*
GO:0050794	regulation of cellular process	31	10484	0.0050	*AIMP2, CCDC47, NOTCH2, ABCC9, CREBBP, SMARCB1, KCNH1, SETBP1, NIPBL, WRN, LTBP3, USP9X, ARID1A, SMC1A, SMARCE1, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, KDM6A, ABCA5, NFIX, SMARCD2, SMARCA4, TAF6, CCBE1, FGFR2, KMT2A, SLC25A24, TWIST2*
GO:0016070	RNA metabolic process	16	3430	0.0053	*AIMP2, NOTCH2, CREBBP, SMARCB1, NIPBL, ARID1A, ARID1B, BCL11B, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, TAF6, KMT2A, TWIST2*
GO:0043933	protein-containing complex subunit organization	11	1770	0.0059	*AIMP2, ADAMTS2, CREBBP, SMARCB1, SNX14, ARID1A, SMARCE1, ABCA5, SMARCD2, SMARCA4, KMT2A*
GO:0051851	modification by host of symbiont morphology or physiology	3	71	0.0059	*SMARCB1, SMC3, SMARCA4*
GO:1901576	organic substance biosynthetic process	19	4656	0.0060	*NANS, AIMP2, NOTCH2, CREBBP, SMARCB1, NIPBL, WRN, ARID1A, ARID1B, BCL11B, MAP3K7, FLNA, NFIX, SMARCD2, SMARCA4, TAF6, FGFR2, KMT2A, TWIST2*

GO:0003016	respiratory system process	2	14	0.0062	*KDM6A, CCBE1*
GO:2001224	positive regulation of neuron migration	2	14	0.0062	*NIPBL, FLNA*
GO:0008152	metabolic process	29	9569	0.0072	*NANS, AIMP2, CCDC47, ADAMTS2, NOTCH2, CREBBP, SMARCB1, KCNH1, NIPBL, WRN, SNX14, USP9X, ARID1A, SMC1A, IDS, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, KDM6A, NFIX, SMARCD2, MAN2B1, SMARCA4, TAF6, FGFR2, KMT2A, TWIST2*
GO:0007064	mitotic sister chromatid cohesion	2	16	0.0075	*NIPBL, SMC1A*
GO:0043923	positive regulation by host of viral transcription	2	17	0.0083	*SMARCB1, SMARCA4*
GO:0006259	DNA metabolic process	7	773	0.0088	*SMARCB1, WRN, SMC1A, BCL11B, SMC3, NFIX, KMT2A*
GO:0048524	positive regulation of viral process	3	85	0.0088	*SMARCB1, SMC3, SMARCA4*
GO:0031058	positive regulation of histone modification	3	86	0.0089	*SMARCB1, NIPBL, KMT2A*
GO:0071704	organic substance metabolic process	28	9135	0.0089	*NANS, AIMP2, CCDC47, ADAMTS2, NOTCH2, CREBBP, SMARCB1, KCNH1, NIPBL, WRN, USP9X, ARID1A, SMC1A, IDS, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, KDM6A, NFIX, SMARCD2, MAN2B1, SMARCA4, TAF6, FGFR2, KMT2A, TWIST2*
GO:0006366	transcription by RNA polymerase II	7	784	0.0093	*NOTCH2, CREBBP, BCL11B, FLNA, NFIX, TAF6, KMT2A*
GO:0048557	embryonic digestive tract morphogenesis	2	19	0.0096	*NIPBL, FGFR2*
GO:0035295	tube development	7	793	0.0097	*AIMP2, ADAMTS2, NIPBL, ARID1A, KDM6A, CCBE1, FGFR2*
GO:1901673	regulation of mitotic spindle assembly	2	20	0.0104	*SMC1A, SMC3*
GO:0000122	negative regulation of transcription by RNA polymerase II	7	809	0.0105	*CREBBP, NIPBL, USP9X, ARID1A, NFIX, SMARCA4, FGFR2*
GO:0051052	regulation of DNA metabolic process	5	381	0.0105	*WRN, USP9X, SMC1A, SMC3, KMT2A*
GO:0016573	histone acetylation	3	96	0.0112	*CREBBP, MAP3K7, KMT2A*
GO:0043902	positive regulation of multi-	5	394	0.0116	*CREBBP, SMARCB1, SMC3, MAP3K7, SMARCA4*

	organism process				
GO:0048731	system development	17	4144	0.0116	*AIMP2, ADAMTS2, NOTCH2, SMARCB1, NIPBL, WRN, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, FLNA, KDM6A, SMARCA4, CCBE1, FGFR2, KMT2A*
GO:0009653	anatomical structure morphogenesis	11	1992	0.0125	*NOTCH2, CREBBP, KCNH1, NIPBL, USP9X, ARID1A, BCL11B, FLNA, KDM6A, CCBE1, FGFR2*
GO:0051090	regulation of DNA-binding transcription factor activity	5	403	0.0125	*SMARCB1, MAP3K7, FLNA, SMARCA4, TAF6*
GO:0045944	positive regulation of transcription by RNA polymerase II	8	1104	0.0127	*CREBBP, SMARCB1, NIPBL, BCL11B, NFIX, SMARCA4, FGFR2, KMT2A*
GO:0003007	heart morphogenesis	4	235	0.0130	*NOTCH2, NIPBL, KDM6A, FGFR2*
GO:0045595	regulation of cell differentiation	10	1695	0.0132	*NOTCH2, CREBBP, NIPBL, LTBP3, BCL11B, FLNA, ABCA5, FGFR2, KMT2A, TWIST2*
GO:0048568	embryonic organ development	5	417	0.0137	*NIPBL, ARID1A, KDM6A, FGFR2, KMT2A*
GO:0048333	mesodermal cell differentiation	2	26	0.0144	*KDM6A, FGFR2*
GO:0009314	response to radiation	5	425	0.0147	*CREBBP, NIPBL, WRN, SMC1A, KMT2A*
GO:0018205	peptidyl-lysine modification	4	250	0.0153	*CREBBP, MAP3K7, KDM6A, KMT2A*
GO:0043921	modulation by host of viral transcription	2	27	0.0153	*SMARCB1, SMARCA4*
GO:0052472	modulation by host of symbiont transcription	2	27	0.0153	*SMARCB1, SMARCA4*
GO:0007059	chromosome segregation	4	253	0.0155	*NIPBL, USP9X, SMC1A, SMC3*
GO:0007420	brain development	6	650	0.0156	*NIPBL, WRN, ARID1A, BCL11B, FLNA, FGFR2*
GO:0001704	formation of primary germ layer	3	115	0.0157	*ARID1A, KDM6A, FGFR2*
GO:0048869	cellular developmental process	15	3533	0.0165	*AIMP2, NOTCH2, SMARCB1, KCNH1, NIPBL, WRN, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, FLNA, KDM6A, FGFR2, TWIST2*
GO:1904837	beta-catenin-TCF complex assembly	2	29	0.0165	*CREBBP, SMARCA4*
GO:0008285	negative regulation of cell population proliferation	6	669	0.0175	*AIMP2, SMARCB1, BCL11B, TAF6, FGFR2, KMT2A*

GO:0051568	histone H3-K4 methylation	2	32	0.0192	*KDM6A, KMT2A*
GO:0072175	epithelial tube formation	3	128	0.0200	*ARID1A, KDM6A, FGFR2*
GO:0048562	embryonic organ morphogenesis	4	279	0.0204	*NIPBL, ARID1A, KDM6A, FGFR2*
GO:0051053	negative regulation of DNA metabolic process	3	134	0.0219	*SMC1A, SMC3, KMT2A*
GO:0007507	heart development	5	485	0.0223	*NOTCH2, NIPBL, ARID1A, KDM6A, FGFR2*
GO:0033554	cellular response to stress	9	1553	0.0224	*CCDC47, CREBBP, SMARCB1, NIPBL, WRN, SMC1A, SMC3, MAP3K7, SLC25A24*
GO:0140014	mitotic nuclear Division	3	136	0.0224	*NIPBL, SMC1A, FLNA*
GO:0048513	animal organ development	13	2926	0.0230	*AIMP2, ADAMTS2, NOTCH2, NIPBL, WRN, ARID1A, BCL11B, FLNA, KDM6A, SMARCA4, CCBE1, FGFR2, KMT2A*
GO:0071560	cellular response to transforming growth factor beta stimulus	3	140	0.0237	*USP9X, MAP3K7, FGFR2*
GO:0016331	morphogenesis of embryonic epithelium	3	141	0.0240	*ARID1A, KDM6A, FGFR2*
GO:0040017	positive regulation of locomotion	5	503	0.0249	*NIPBL, SMC3, FLNA, CCBE1, TWIST2*
GO:0042127	regulation of cell population proliferation	9	1594	0.0256	*AIMP2, SMARCB1, KCNH1, LTBP3, BCL11B, FLNA, TAF6, FGFR2, KMT2A*
GO:0035108	limb morphogenesis	3	147	0.0262	*CREBBP, NIPBL, FGFR2*
GO:0007423	sensory organ development	5	515	0.0266	*NIPBL, ARID1A, BCL11B, SMARCA4, FGFR2*
GO:0071478	cellular response to radiation	3	153	0.0285	*CREBBP, NIPBL, WRN*
GO:0010941	regulation of cell death	9	1638	0.0296	*AIMP2, NOTCH2, CREBBP, WRN, BCL11B, FLNA, FGFR2, SLC25A24, TWIST2*
GO:0006367	transcription initiation from RNA polymerase II promoter	3	162	0.0317	*NOTCH2, CREBBP, TAF6*
GO:0022414	reproductive process	8	1350	0.0317	*ADAMTS2, NIPBL, USP9X, ARID1A, SMC1A, SMC3, FLNA, FGFR2*
GO:0030154	cell differentiation	14	3457	0.0317	*AIMP2, NOTCH2, SMARCB1, KCNH1, NIPBL, USP9X, ARID1A, SMARCE1, ARID1B, BCL11B, FLNA, KDM6A, FGFR2, TWIST2*

GO:0048598	embryonic morphogenesis	5	545	0.0317	*CREBBP, NIPBL, ARID1A, KDM6A, FGFR2*
GO:0048701	embryonic cranial skeleton morphogenesis	2	46	0.0317	*NIPBL, FGFR2*
GO:0001654	eye development	4	339	0.0328	*NIPBL, ARID1A, BCL11B, SMARCA4*
GO:0003205	cardiac chamber development	3	166	0.0328	*NOTCH2, ARID1A, FGFR2*
GO:0048589	developmental growth	4	340	0.0328	*NIPBL, USP9X, KDM6A, FGFR2*
GO:0072359	circulatory system development	6	807	0.0335	*NOTCH2, NIPBL, ARID1A, KDM6A, CCBE1, FGFR2*
GO:0021879	forebrain neuron differentiation	2	50	0.0342	*BCL11B, FGFR2*
GO:0016570	histone modification	4	347	0.0344	*CREBBP, MAP3K7, KDM6A, KMT2A*
GO:0050793	regulation of developmental process	11	2416	0.0367	*NOTCH2, CREBBP, NIPBL, LTBP3, BCL11B, FLNA, ABCA5, CCBE1, FGFR2, KMT2A, TWIST2*
GO:0030278	regulation of ossification	3	181	0.0386	*NIPBL, FGFR2, TWIST2*
GO:0018193	peptidyl-amino acid modification	6	842	0.0387	*CREBBP, KCNH1, MAP3K7, KDM6A, FGFR2, KMT2A*
GO:0030900	forebrain development	4	366	0.0392	*ARID1A, BCL11B, FLNA, FGFR2*
GO:0031060	regulation of histone methylation	2	58	0.0422	*SMARCB1, KMT2A*
GO:0051716	cellular response to stimulus	20	6212	0.0422	*CCDC47, NOTCH2, ABCC9, CREBBP, SMARCB1, KCNH1, NIPBL, WRN, USP9X, ARID1A, SMC1A, ARID1B, BCL11B, SMC3, MAP3K7, FLNA, KDM6A, SMARCA4, FGFR2, SLC25A24*
GO:0009887	animal organ morphogenesis	6	865	0.0425	*NOTCH2, NIPBL, ARID1A, BCL11B, KDM6A, FGFR2*
GO:0031401	positive regulation of protein modification process	7	1149	0.0425	*AIMP2, NOTCH2, SMARCB1, NIPBL, MAP3K7, FGFR2, KMT2A*
GO:0035239	tube morphogenesis	5	615	0.0452	*NIPBL, ARID1A, KDM6A, CCBE1, FGFR2*
GO:0006950	response to stress	13	3267	0.0459	*CCDC47, ABCC9, CREBBP, SMARCB1, NIPBL, WRN, SMC1A, ARID1B, SMC3, MAP3K7, FLNA, FGFR2, SLC25A24*
GO:0002223	stimulatory C-type lectin receptor signaling pathway	2	62	0.0463	*CREBBP, MAP3K7*
GO:0009790	embryo development	6	890	0.0475	*CREBBP, NIPBL, ARID1A, KDM6A, FGFR2, KMT2A*
GO:0009967	positive regulation of signal	8	1493	0.0477	*NOTCH2, CREBBP, SMARCB1, MAP3K7, FLNA, SMARCA4,*

	transduction				*CCBE1, FGFR2*
GO:0009880	embryonic pattern specification	2	64	0.0481	*KDM6A, FGFR2*
GO:0032270	positive regulation of cellular protein metabolic process	8	1496	0.0481	*AIMP2, NOTCH2, SMARCB1, NIPBL, MAP3K7, CCBE1, FGFR2, KMT2A*
GO:0071479	cellular response to ionizing radiation	2	64	0.0481	*NIPBL, WRN*
GO:0071277	cellular response to calcium ion	2	65	0.0489	*KCNH1, SLC25A24*

Supplementary Table 2. Activated pathways characterized with syndromes with hypertrichosis and dental anomalies-containing-genes.

	Term description	Observed gene count	Background gene count	False discovery rate	Matching proteins in your network
hsa05225	Hepatocellular carcinoma	6	163	5.77e-05	*SMARCB1, ARID1A, SMARCE1, ARID1B, SMARCD2, SMARCA4*
hsa04714	Thermogenesis	6	228	0.00019	*SMARCB1, ARID1A, SMARCE1, ARID1B, SMARCD2, SMARCA4*
hsa04110	Cell cycle	3	123	0.0433	*CREBBP, SMC1A, SMC3*

References

[1] Wendelin DS, Pope DN, Mallory SB. Hypertrichosis. J Am Acad Dermatol. 2003; 48(2):161–79. doi: 10.1067/mjd.2003.100.

[2] Brooks JK. A review of syndromes associated with blue sclera, with inclusion of malformations of the head and neck. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018; 126(3):252-263. doi: 10.1016/j.oooo.2018.05.012.

[3] de La Dure-Molla M, Fournier BP, Manzanares MC, Acevedo AC, Hennekam RC, Friedlander L, et al. Elements of morphology: standard terminology for the teeth and classifying genetic dental disorders. Am J Med Genet A. 2019;179(10):1913-1981. doi: 10.1002/ajmg.a.61316.

[4] Pispa J, Thesleff I. Mechanisms of ectodermal organogenesis. Dev Biol. 2003; 262(2):195-205. doi: 10.1016/s0012-1606(03)00325-7

[5] Ahn Y. Signaling in tooth, hair, and mammary placodes. Curr Top Dev Biol. 2015; 111:421-459. doi: 10.1016/bs.ctdb.2014.11.013.

[6] Eliason S, Sharp T, Sweat M, Sweat YY, Amendt BA. Ectodermal Organ Development Is Regulated by a microRNA-26b-Lef-1-Wnt Signaling Axis. Front Physiol. 2020; 11:780. doi: 10.3389/fphys.2020.00780.

[7] Sasaki T, Ito Y, Xu X, Han J, Bringas Junior P, Maeda T, et al. LEF1 is a critical epithelial survival factor during tooth morphogenesis. Dev Biol. 2005; 278(1):130-43. doi: 10.1016/j.ydbio.2004.10.021.

[8] Cao H, Jheon A, Li X, Su Z, Wang J, Florez S, et al. The Pitx2: miR-200c/141: noggin pathway regulates Bmp signaling and ameloblast differentiation. Development. 2013; 40(16):3348-59. doi: 10.1242/dev.089193.

[9] Järvinen E, Shimomura-Kuroki J, Balic A, Jussila M, Thesleff I. Mesenchymal Wnt/β-catenin signaling limits tooth number. Development. 2018;145(4): dev158048. Published 2018 Feb 21. doi:10.1242/dev.158048

[10] Hawkshaw NJ, Hardman JA, Haslam IS, Shahmalak A, Gilhar A, Lim X, et al. Identifying novel strategies for treating human hair loss disorders: Cyclosporine A suppresses the Wnt inhibitor, SFRP1, in the dermal papilla of human scalp hair follicles. PLoS Biol. 2018;16(5):e2003705. https://doi.org/10.1371/journal.pbio.2003705

[11] Taniguchi K, Roberts LR, Aderca IN, Dong X, Qian C, Murphy LM, et al. Mutational spectrum of β-catenin, AXIN1, and AXIN2 in hepatocellular carcinomas and hepatoblastomas. Oncogene. 2002; 21(31):4863-71. doi: 10.1038/sj.onc.1205591.

[12] Alazami AM, Patel N, Shamseldin HE, Anazi S, Al-Dosari MS, Alzahrani F, et al. Accelerating novel candidate gene discovery in neurogenetic disorders via whole-exome

sequencing of prescreened multiplex consanguineous families. Cell reports. 2015; 10(2):148-161. doi: 10.1016/j.celrep.2014.12.015.

[13] Martins F, Ortega KL, Hiraoka C, Ricardo P, Magalhaes M. Oral and dental abnormalities in Barber–Say syndrome. Am J Med Genet A. 2010; 152A(10):2569-2573. doi: 10.1002/ajmg.a.32898.

[14] Masmoudi A, Marrakchi S, Kamoun H, Chaaben H, Salah GB, Salah RB, et al. Clinical and laboratory findings in 8 patients with Bloom's syndrome. J Dermatol Case Rep. 2012; 6(1):29-33. doi: 10.3315/jdcr.2012.1086

[15] Scurr I, Wilson L, Lees M, Robertson S, Kirk E, Turner A, et al. Cantu syndrome: report of nine new cases and expansion of the clinical phenotype. Am J Med Genet A. 2011; 155A(3):508-518. doi: 10.1002/ajmg.a.33885.

[16] Tan TY, Aftimos S, Worgan L, Susman R, Wilson, M, Ghedia S, et al. Phenotypic expansion and further characterisation of the 17q21. 31 microdeletion syndrome. J Med Genet. 2019; 46(7):480-489. doi: 10.1136/jmg.2008.065391.

[17] Mannino EA, Miyawaki H, Santen G, Schrier Vergano SA. First data from a parent-reported registry of 81 individuals with Coffin–Siris syndrome: Natural history and management recommendations. Am J Med Genet A. 2018; 176(11):2250-2258. doi: 10.1002/ajmg.a.40471

[18] Guadagni MG, Cetrullo N, Piana G. Cornelia de Lange syndrome: description of the orofacial features and case report. Eur J Paediatr Dent. 2008;9(4):9-13.

[19] Torun GS, Akbulut A. Crouzon syndrome with multiple supernumerary teeth. Niger J Clin Pract. 2017; 20(2):261-263.doi: 10.4103/1119-3077.187332.

[20] Bertola DR, Antequera R, Rodovalho MJ, Honjo RS, Albano LMJ, Furquim IM, et al. Brachyolmia with amelogenesis imperfecta: further evidence of a distinct entity. Am. J. Med. Genet. 2009; 149A(3):532-534.doi: 10.1002/ajmg.a.32661.

[21] Hansen J, Mohr J, Burki S, Lemke JR.A case of cohesinopathy with a novel de-novo SMC1A splice site mutation**.**Clin. Dysmorph. 2013; 22: 143-145. doi: 10.1097/MCD.0b013e3283645439.

[22] Peled A, Sarig O, Samuelov L, Bertolini M, Ziv L, Weissglas-Volkov D, et al. Mutations in TSPEAR, encoding a regulator of Notch signaling, affect tooth and hair follicle morphogenesis. PLoS Genet. 2016; 12(10): e1006369.

[23] Malfait F, De Coster P, Hausser I, van Essen AJ, Franck P, Colige A, et al. The natural history, including orofacial features of three patients with Ehlers–Danlos syndrome, dermatosparaxis type (EDS type VIIC). Am J Med Genet A. 2004; 131(1):18-28. doi: 10.1371/journal.pgen.1006369.

[24] Sharif S, Donnai D. Filippi syndrome: two cases with ectodermal features, expanding the phenotype. Clin Dysmorphol. 2004;13(4):221-226. doi: 10.1097/00019605-200410000-00004.

[25] Rosti RO, Karaer K, Karaman B, Torun D, Guran S, Bahce M. Gorlin–chaudhry–moss syndrome revisited: Expanding the phenotype. Am J Med Genet A. 2013; 161(7):1737-1742. doi: 10.1002/ajmg.a.35954.

[26] Wade EM, Daniel PB, Jenkins ZA, McInerney-Leo A, Leo P, Morgan T, et al. Mutations in MAP3K7 that alter the activity of the TAK1 signaling complex cause frontometaphyseal dysplasia. Am. J. Hum. Genet. 2016; 99(2):392-406. doi: 10.1016/j.ajhg.2016.05.024.

[27] Sun M, Li N, Dong W, Chen Z, Liu Q, Xu, et al. Copy-number mutations on chromosome 17q24.2-q24.3 in congenital generalized hypertrichosis terminalis with or without gingival hyperplasia. Am. J. Hum. Genet. 2009; 84(6):807-813. doi: 10.1016/j.ajhg.2009.04.018.

[28] Browne RM, Byrne JP. Dental dysplasia in incontinentia pigmenti achromians (Ito). An unusual form. Br Dent J. 1976; 140(6):211–214. doi: 10.1038/sj.bdj.4803735.

[29] O'Reilly MA, Shaw DG. Hajdu-Cheney syndrome. Ann Rheum Dis. 1994; 53(4):276.

[30] Lakshminarayana G, Mathew A, Rajesh R, Kurien G, Unni VN. Hennekam lymphangiectasia syndrome. Indian J Nephrol. 2011; 21(4): 273–275. doi: 10.4103/0971-4065.78068

[31] Punwani D, Zhang Y, Yu J, Cowan MJ, Rana S, Kwan A, et al. Multisystem anomalies in severe combined immunodeficiency with mutant BCL11B. New Eng. J. Med. 2016; 375(22):2165-2176. doi: 10.1056/NEJMoa1509164.

[32] Silva-Andrade N, López-Ortega K, Gallottini M. Orofacial features and medical profile of eight individuals with Kabuki syndrome. Med Oral Patol Oral Cir Bucal. 2019; 24(5):e630. doi: 10.4317/medoral.22982

[33] Shukla A, Bhowmik AD, Hebbar M, Rajagopal KV, Girisha KM, Gupta N, et al. Homozygosity for a nonsense variant in AIMP2 is associated with a progressive neurodevelopmental disorder with microcephaly, seizures, and spastic quadriparesis. J Hum Genet. 2018; 63(1):19-25. doi: 10.1038/s10038-017-0363-1

[34] Miranda PG, Henriques JCG, Paulo LFB, Guedes CDCFV, Mitri FF, Silva CJ. Jaffe-Lichtenstein Syndrome Associated with a Simple Bone Cyst: Unprecedented Rare Case Report. *Braz Dent J*. 2020;31(5):557-561. doi:10.1590/0103-6440202003158

[35] Verloes A, Lesenfants S. A new form of mandibulofacial dysostosis with macroblepharon and macrostomia. Clin Dysmorphol. 1997; 6(1):21-24.

[36] Malm D, Nilssen Ø. Alpha-mannosidosis. Orphanet J Rare Dis. 2018; 3(1):1-10

[37] Shaw AC, van Balkom ID, Bauer M, et al. Phenotype and natural history in Marshall-Smith syndrome. Am J Med Genet *A*. 2010;152A (11):2714-2726. doi:10.1002/ajmg.a.33709

[38] Reijnders MRF, Zachariadis V, Latour B, Jolly L, Mancini GM, Pfundt R, et al. De novo loss-of-function mutations in USP9X cause a female-specific recognizable syndrome with developmental delay and congenital malformations. Am. J. Hum. Genet. 2016; 98(2):373-381. doi: 10.1016/j.ajhg.2015.12.015.

[39] Torres RO, Pintor AVB, Guedes FR, Cevidanes LHS, Freitas-Fernandes LB, de Oliveira Ruellas AC, et al. Three-dimensional dental and craniofacial manifestations in patients with late diagnosis of mucopolysaccharidosis type II: report of 2 cases. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018; 126:e35-e39.doi: 10.1016/j.oooo.2018.03.016.

[40] Mehawej C, Hoischen A, Farah RA, Marey I, David M, Stora S, et al. Homozygous mutation in ELMO2 may cause Ramon syndrome. Clin Genet. 2018; 93(3):703-706. doi: 10.1111/cge.13166.

[41] Bloch-Zupan A, Stachtou J, Emmanouil D, Arveiler B, Griffiths D, Lacombe D. Oro-dental features as useful diagnostic tool in Rubinstein–Taybi syndrome. Am J Med Genet A. 2007; 143(6):570-573. doi: 10.1002/ajmg.a.31622.

[42] Heggie C, Gartshores L. Diagnosis, Management and Follow-Up of a Rare Regional Developmental Disorder: Segmental Odontomaxillary Dysplasia. J Dent Child. 2020; 87(1):39-43.

[43] Cooke ME, Davidson LE, Livesey SL. Schinzel–Giedion syndrome: interesting facial and orodental features, and dental management. Int J Paediatr Dent. 2002; 12(1):66-72. doi: 10.1046/j.0960-7439.2001.00325.x.

[44] Witzel M, Petersheim D, Fan Y, Bahrami E, Racek T, Rohlfs M, et al. Chromatin-remodeling factor SMARCD2 regulates transcriptional networks controlling differentiation of neutrophil granulocytes. Nature Genet. 2017; 49:742-752.

[45] Sousa SB, Ramos F, Garcia P, Pais RP, Paiva C, Beales PL, et al. Intellectual disability, coarse face, relative macrocephaly, and cerebellar hypotrophy in two sisters. Am J Med Genet A. 2014; 164(1):10-14. doi: 10.1002/ajmg.a.36235

[46] Burrage LC, Reynolds JJ, Baratang NV, Phillips JB, Wegner J, McFarquhar A, et al. Bi-allelic variants in TONSL cause SPONASTRIME dysplasia and a spectrum of skeletal dysplasia phenotypes. Am J Hum Genet 2019; 104(3):422-438. doi: 10.1016/j.ajhg.2019.01.007.

[47] Morimoto M, Waller-Evans H, Ammous Z, Song X, Strauss KA, Pehlivan D, et al. Bi-allelic CCDC47 variants cause a disorder characterized by woolly hair, liver dysfunction, dysmorphic features, and global developmental delay. Am J Hum Genet. 2018; 103(5):794-807. doi: 10.1016/j.ajhg.2018.09.014.

[48] Tenorio J, Mansilla A, Valencia M, Martinez-Glez V, Romanelli V, et al. A new overgrowth syndrome is due to mutations in RNF125. Hum. Mutat. 2014; 35(12):1436-1441. doi: 10.1002/humu.22689.

[49] Miyake N, Tsurusaki Y, Koshimizu E, Okamoto N, Kosho T, Brown NJ, et al. Delineation of clinical features in Wiedemann-Steiner syndrome caused by KMT2A mutations. Clin. Genet. 2016; 89: 115-119. doi: 10.1111/cge.12586

[50] Stefanova M, Atanassov D, Krastev T, Fuchs S, Kutsche, K. Zimmermann–Laband syndrome associated with a balanced reciprocal translocation t (3; 8)(p21. 2; q24. 3) in mother and daughter: Molecular cytogenetic characterization of the breakpoint regions. Am J Med Genet A. 2003; 117A(3):289-294. doi: 10.1002/ajmg.a.10174.

4.2. Produto Técnico

4.2.1 Vídeo informativo -Pitch

https://www.youtube.com/watch?v=13OtuuAgYNc

5. CONCLUSÕES

Após a realização do estudo e de acordo com os objetivos específicos pode-se concluir que:

1. A hipertricose pode estar associada a uma doença genética multissistêmica. Tiveram destaque o acometimento da cabeça e pescoço (80,16%), sistema esquelético (78,51%), sistema nervoso (73,55%) e deficiência intelectual (52,06%). Outras categorias acometidas foram abdome (42,97%), sistema geniturinário (39,66%), anomalias dentárias (32,23%), sistema cardiovascular (32,23%), mortalidade até infância (18,18%), endocrinopatias (14,04%) e associação com neoplasia maligna (8,26%). A herança foi autossômica recessiva em 44.62%, autossômica dominante em 36.36% e outras em 20.66%.

2. A hipertricose foi associada a anomalias dentárias em 32,23% das síndromes genéticas avaliadas. Tiveram destaque a agenesia dentária, presente em 41,02% desses distúrbios, seguido por atraso na erupção dentária e espaçamento irregular. Foram identificados genes causadores em 33 de 39 distúrbios. Destes, foram identificados 39 genes, mas apenas 38 genes foram reconhecidos e analisados pela análise STRING, que identificou 148 processos biológicos e 3 vias estastisticamente significativos.

3. Foi elaborado um vídeo informativo, tipo Pitch, direcionado ao público leigo, em linguagem acessível, sobre hipertricose e as características clínicas das doenças genéticas associadas.

6. CONSIDERAÇÕES FINAIS

O estudo da hipertricose é um desafio para o profissional de saúde, porque são muitas as causas que podem estar associadas. Quando ela é integrante do fenótipo de várias doenças, sua incidência aumenta, e pode não se tratar de uma característica clínica rara. O fenótipo dos distúrbios de origem genética apresentaexpressividade variável heterogeneidade etiológicae nem sempre é possível fazer a correlação genótipo-fenótipo, o que dificulta o processo investigativo.

Os termos hipertricose e hirsutismo muitas vezes são utilizados por diferentes autores para se referirem à uma mesma doença, o que evidencia uma falta de padronização. A investigação reforça a valorização do exame clínico minucioso, pela amanese e exame físico bem realizados. As categorias de acometimento clínico mais frequentemente identificadas nosdistúrbios genéticos com hipertricose foram alterações da cabeça e pescoço, sistema esquelético e sistema nervoso, com destaque para deficiência intelectual.

Esta pesquisa tem limitações por se tratar de uma revisão de literatura, muitas vezes baseada em relatos de casos, com número pequeno de pacientes, característica de doenças raras.Mais pesquisas são necessárias para a construção de ferramentas de auxílio à pratica clínica para o desafiante estudo de doenças genéticas, sobretudo relacionado à hipertricose, um sinal cutâneo que pode levar ao diagnóstico de uma doença genética grave, multissistêmica e que pode estar relacionadaa doenças malignas.

REFERÊNCIAS

ADAM, M. P.; *et al.*Marshall-Smith syndrome: natural history and evidence of an osteochondrodysplasia with connective tissue abnormalities. *Am. J. Med. Genet*., v.137, n.2, p.117-124, 2005.

ALAWI, F. Using rare diseases as teaching models to increase awareness. *Oral Surg Oral Med Oral Pathol Oral Radiol*., v.128, n.2, p.99-100, 2019.

ALDERS, M., *et al.* Hennekam syndrome can be caused by FAT4 mutations and be allelic to Van Maldergem syndrome. *Hum. Genet*., v.133, p.1161-1167, 2014.

ALONSO, L.; *et al*. Sgk3 links growth factor signaling to maintenance of progenitor cells in the hair follicle. *J. Cell Biol.,* v.170, n.4, p.559-570, 2005.

ALONSO, L.; FUCHS, E. The hair cycle. *J Cell Sci.*, v.119, p.391-393, 2006.

BADYAL, D. Orphan diseases and drugs. *Ind J Pharmacol*, v.38, n.4, p.299-300, 2006.

BATTAGLIA, A.; *et al*. New autosomal recessive syndrome of mental retardation, coarse face, microcephaly, epilepsy and skeletal abnormalities. *Clin. Dysmorph*., v.5, p.41-47, 1996.

BEIGHTON, P. Congenital hypertrichosis lanuginosa. *Arch Dermatol*., v.101, n.6, p.669–672, 1970.

BERTOLINO, A.; *et al*. *Dermatology in general medicine*. New York: McGraw-Hill; p.671-96, 1993.

BÍBLIA, A. T. Gênesis. *Sagrada Bíblia Católica*: Antigo e Novo Testamentos. Disponível em: <https://www.bibliaon.com/genesis_25/ >.Acesso em: 10 fev. 2020.

BLANPAIN, C.; *et al*. Self-renewal, multipotency, and the existence of two cell populations within an epithelial stem cell niche. *Cell*., v 118, n.5, p.635-648, 2004.

BLUME-PEYTAVI, U., *et alHair Growth and Disorders.* 1.ed. Berlim: Springer-Verlag, 2008. 571p.

BONDESON, J.; MILES, A. E. Julia Pastrana, the nondescript: an example of congenital, generalized hypertrichosis terminalis with gingival hyperplasia. *Am J Med Genet*., v.47, n.2, p.198–212, 1993.

BRASIL. Ministério da Saúde. *Doenças raras*: o que são, causas, tratamento, diagnóstico e prevenção. Disponível em: < www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z-1/d/doencas-raras >.Acesso em: 8 mar. 2021.

BREATHNACH, A.S.; ROBINS, E.J. Ultrastructure of Developing Hair Tract and Hair Canal in the Human Fetus. *In*: ORFANOS, C.E.; MONTAGNA, W., STUTTGEN, G.; (eds) *Hair research. Springer Berlin Heidelberg New York* Research, Hamburg, March, 1981.

CALLAHAN, C. A.; *et al*. MIM/BEG4, a Sonic hedgehog-responsive gene that potentiates Gli-dependent transcription. *Genes Dev.*,v.18, n.22, p. 2724-2729, 2004.

CERUTI, J.M.; LEIROS, G.J.; BALANA, M.E. Androgens and androgen receptor action in skin and hair follicles. *Mol. Cell. Endocrinol*., v.465, p.122–133, 2018.

CHATURVEDI, A.P.; DEHM, S.M. Androgen receptor dependence. *Adv. Exp. Med. Biol*, v.1210, p.333–350, 2019.

CHEMIN, J.; *et al*. De novo mutation screening in childhood-onset cerebellar atrophy identifies gain-of-function mutations in the CACNA1G calcium channel gene. *Brain,* v.141, p.1998-2013, 2018.

CHRISTOPH, T.; *et al*. The human hair follicle immune system: cellular composition and immune privilege. *Br J Dermatol*.,v.142, n.5, p.862–873, 2000.

CHUDLEY, A. E.; *et al*. X-linked mental retardation syndrome with seizures, hypogammaglobulinemia, and progressive gait disturbance is regionally mapped between Xq21.33 and Xq23. *Am. J. Med. Genet*., v.85, p. 255-262, 1999.

CHUNMEI, L.; *et al.* UBR7 functions with UBR5 in the Notch signaling pathway and is involved in a neurodevelopmental syndrome with epilepsy, ptosis, and hypothyroidism. *Am. J. Hum. Genet*., v.108, n.1, p.134-147, 2021.

COENE, K. L. M., *et al*. OFD1 is mutated in X-linked Joubert syndrome and interacts with LCA5-encoded lebercilin. *Am. J. Hum. Genet*., v.85, p.465-481, 2009.

COTSARELIS, G.; BOTCHKAREV, V.A. Biology of hair follicles. In: Goldsmith, L.A.; *et al. Fitzpatrick's Dermatology in General Medicine*. New York: McGraw Hill, 2008, p.739–749.

COURTOIS. M.; *et al*. Periodicity in the growth and shedding of hair. *Br J Dermatol*., v.134, n.1, p.47–54, 1996.

COUSIN, J.; *et al.* Dysplasie pelvi-scapulaire familiale avec anomalies epiphysaires, nanisme et dysmorphies: un nouveau syndrome? *Arch. Franc. Pediat*., v.39, p.173-175, 1982.

CYRUS, S.S.; *et al*.Rare SUZ12 variants commonly cause an overgrowth phenotype. *Am. J. Med. Genet*., v.181, n.4, p.532-547, 2019.

DANFORTH, C. H. Studies on hair, with special reference to hypertrichosis. *Arch. Derm. Syph*., v.11, n.5, p.494-508, 1925.

DE BERKER, D.A.R.; MESSENGER, A.G.; SINCLAIR, R.D. Disorders of hair. *In:* BURNS, T.; *et al. Rook's Text- book of Dermatology*. 7ed. Massachusetts: Blackwell, 2004, p.91-3.

DESANTO, C.; *et al*. WAC loss-of-function mutations cause a recognizable syndrome characterised by dysmorphic features, developmental delay and hypotonia and recapitulate 10p11.23 microdeletion syndrome. *J. Med. Genet*., v.52, p.754-761, 2015.

DUGGINS, O.H.; TROTTER, M. Age changes in head hair from birth to maturity: medullation in hair of children. *Am J Phys Anthropol*., v.8, n.3, p.399-415, 1950.

EBLING, F.G.E. The biology of hair. *Dermatol Clin*.,v.5, n.3, p.467-480, 1987.

ELLIOTT, K.; STEPHENSON, T.J.; MESSENGER, A.G. Differences in hair follicle dermal papilla volume are due to extracellular matrix volume and cell number: implications for the control of hair follicle size and androgen responses. *J Invest Dermatol*., v.113, n.6, p.873–877, 1999.

ELSTON,D.M. Congenital hypertrichosis lanuginosa. 2018. Disponível em: <http://emedicine.medscape.com/article/1072987-overview>. Acesso em: 03 nov. 2020.
ENNS, G. M., *et al.* Clinical course and biochemistry of sialuria*. J. Inherit. Metab. Dis*., v.24, p. 328-336, 2001.

FANTAUZZO, K. A., *et al*. Trps1 and its target gene Sox9 regulate epithelial proliferation in the developing hair follicle and are associated with hypertrichosis. *PLoS Genetics*, v. 8, n.11, e1003002, 2012.

FIOTZIK, K.; *et al.* Human scalp hair follicles are both a target and a source of prolactin, which serves as an autocrine and/or paracrine promoter of apoptosis-driven hair follicle regression. *Am J Pathol*., v.168, n.3, p.748–756, 2006.

FUCHS, E. Scratching the surface of skin development. *Nature*, v.445, n.7130, p.834–842, 2007.

FUCHS, E. Skin stem cells, rising to the surface. *J. Cell Biol*. V.180, n.2, p. 273–284, 2008.

GARCIA-CRUZ, D.; FIGUERA, LE.; CANTU, JM. Inherited hypertrichoses. *Clin Genet*., v.61, n.5, p.321–329, 2002.

GRIGELIONIENE, G.; *et al*. Extending the phenotype of lethal skeletal dysplasia type al Gazali. *Am. J. Med. Genet*., v.155A, 1404-1408, 2011.

GRISART, B.; *et al.* Sandford, R. 17q21.31 microduplication patients are characterised by behavioural problems and poor social interaction. J. *Med. Genet,*.v.46, p. 524-530, 2009.

GULSUNER, S.; *et al*. Homozygosity mapping and targeted genomic sequencing reveal the gene responsible for cerebellar hypoplasia and quadrupedal locomotion in a consanguineous kindred. *Genome Res*., v.21, p.1995-2003, 2011.

HAMILTON, J.B. Age, sex and genetic factors in the regulation of hair growth in man: a comparison of Caucasian and Japanese populations. In: MONTAGNA, W.; ELLIS, R.A (eds). *The biology of hair growth*. Academic Press, New York, 1958, p.399–433.

HANDELSMAN, D.J. Androgen action and pharmacologic uses. In: DEGROOT, L.J.; JAMESON, J. L (eds) *Endocrinology*, 5th edn. WB Saunders, Philadelphia, 2005, p.3121–3138.

HARDY, M.K. The differentiation of hair follicles and hairs in organ culture. In: MONTAGNA, W.; DOBSON, R.L (eds). *Advances in biology of skin volume*, *IX*: hair growth. Pergamon, Oxford, 1969.

HARLAND, D.P. Introduction to Hair Development. In: PLOWMAN, J.; HARLAND, D.; DEB-CHOUDHURY, S. (eds) *The Hair Fibre*: Proteins, Structure and Development. Advances in Experimental Medicine and Biology., v.1054. Springer, Singapore, 2018.

HOFFMANN, R.; *et al*, A. Steroid sulfatase in the human hair follicle concentrates in the dermal papilla. *J. Investig. Dermatol*., v.117, n.6, p.1342–1348, 2001.

HOHL, A.; RONSONI, M. F.; OLIVEIRA, M. D. Hirsutismo: diagnóstico e tratamento. *Arquivos Brasileiros de Endocrinologia & Metabologia*, v.58, n.2, p.97-107, 2014.

HOLBROOK, K. A.; ODLAND, G. F. Structure of the human fetal hair canal and initial hair eruption. *J Invest Dermatol*., v.71, n.6, p.385–390, 1978.

HSU, Y.C; PASOLLI, H.A.; FUCHS, E. Dynamics between stem cells, niche, and progeny in the hair follicle. *Cell*., v.144, n.1, p.92–105, 2011.

INUI, S.; ITAMI, S. Androgen actions on the human hair follicle: perspectives. *Exp Dermatol*., v.22, n.3, p.168-71, 2013.

ISIDOR, B.; *et al*. Truncating mutations in the last exon of NOTCH2 cause a rare skeletal disorder with osteoporosis. *Nature Genet*., 43, p.306-308, 2011.

ITO, T.; *et al.* Collapse and restoration of MHC class-I-dependent immune privilege: exploiting the human hair follicle as a model. *Am J Pathol*., v.164, n.2, p.623–634, 2004.

JAAKKOLA, E.; *et al*. ERCC6 founder mutation identified in Finnish patients with COFS syndrome. Clin. Genet. 78: 541-547, 2010.

KANTHI, A., *et al*. Bi-allelic c.181_183delTGT in BTB domain of KLHL7 is associated with overlapping phenotypes of Crisoni/CISS1-like and Bohring-Opitz like syndrome. *Europ. J. Med. Genet*., v.62, p.103528, 2019.

KARIYA, Y.; *et al*. Sex steroid hormone receptors in human skin appendage and its

neoplasms. *Endocr. J.*, v.*52*, n.3, p.317–325, 2005.

KAUFMAN, K.D.; *et al.* Finasteride in the treatment of men with androgenetic alopecia. Finasteride Male Pattern Hair Loss Study Group. *J Am Acad Dermatol.,* v.39, n.4, p.578–589, 1988.

KIM, S.; *et al*. Localized TWIST1 and TWIST2 basic domain substitutions cause four distinct human diseases that can be modeled in Caenorhabditis elegans. *Hum. Molec. Genet*., v.26, p.2118-2132, 2017.

KRUNIC, A. L., *et al*. Congenital reticular ichthyosiform erythroderma-ichthyosis variegata: a case report and review of the literature. *Acta Derm. Venereol*., v.83, n.1, p. 36-39, 2003.

KRUSZKA, P.; *et al.* Cohesin complex-associated holoprosencephaly. *Brain*, v.142, p. 2631-2643, 2019.

KULESSA, H.; TURK, G.; HOGAN, B. L. Inhibition of Bmp signaling affects growth and differentiation in the anagen hair follicle. *EMBO J.,* v.19, n.24, p.6664-6674, 2000.

LAVKER, R. M.;*et al*. Hair follicle stem cells. *J Investig Dermatol Symp Proc*., v.8, n.1, p.28-38, 2003.

LINDNER, G., *et al.* Analysis of apoptosis during hair follicle regression (catagen). *Am. J. Pathol.,* v.151, n.6, p.1601-1617,1997.

LOWRY, W. E., *et al.*(2005). Defining the impact of beta-catenin/Tcf transactivation on epithelial stem cells. *Genes Dev.,* v.19, n.13, p.1596-1611, 2005.

LUDWIG, E. Classification of the types of andro- 50. genic alopecia (common baldness) arising in the femalesex. *Br J Dermatol*., v.97, n.3, p.249–256, 1977.

LYNFIELD, Y.L. Effect of pregnancy on the humanhair cycle. *J Invest Dermatol* 35, p.323–327, 1960.

MA, L.; *et al.* 'Cyclic alopecia' in Msx2 mutants: defects in hair cycling and hair shaft differentiation. *Development*, v.130, p.379-389, 2003.

MAGEN, D.; *et al*. Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with a loss-of-function mutation in CDK5. Hum. Genet. 134: 305-314, 2015. Note: Erratum: Hum. Genet. 134: 315 only, 2015.

MAO, X.; *et al.* The epilepsy of infancy with migrating focal seizures: identification of de novo mutations of the KCNT2 gene that exert inhibitory effects on the corresponding heteromeric KNa1.1/KNa1.2 potassium channel. *Front. Cell. Neurosci*., v.14, n.1, 2020.

MARSHALL, W.A; TANNER, J.M. Variations in the pattern of pubertal changes in boys. *Arch Dis Child.*, v.45, n.235, p.13–23, 1970.

MARSHALL, W.A.; TANNER, J.M. Variations in pattern of pubertal change in girls. *Arch*

Dis Child., v.44, n.291, p.303, 1969.

MARTELLI D.R.B., MARTELLI JÚNIOR H. Undiagnosed and rare diseases: current challenges, perspectives and contribution of oral cavity examination. *Oral Surg Oral Med Oral Pathol Oral Radiol*., v.30,n.2,p.227-228, 2020.

MCPHAUL, M.J. Mutations that alter androgen function; androgen insensitivity and related disorders. In: DEGROOT, L.J.; JAMESON, J.L. Endocrinology, 5th ed., Section XIV. In: Burger HG (ed) Male reproduction. WB Saunders, Philadelphia, p.3139–3157, 2005.

MINDIKOGLU, A. N.; ERGINEL, A.; CENANI, A. An unknown syndrome of nose deformity, oxycephaly, aplasia of the nasolacrimal ducts, and symmetrical cyst formation on the upper lip in siblings: craniorhiny. *Plast. Reconst. Surg*., v.88, p. 699-702, 1991.

MOCHIDA, G. H.; *et al*. CHMP1A encodes an essential regulator of BMI1-INK4A in cerebellar development. *Nature Genet*., v.44, n.11, p.1260-1264, 2012.

MONTAGNA, W.; PARAKKAL, P.F. *The structure and function of skin*. Academic Press, New York, 1974.

MULLER-ROVER, S., *et al.* A comprehensive guide for the accurate classification of murine hair follicles in distinct hair cycle stages. *J. Invest. Dermatol.,* v.117, n.1, p.3-15, 2001.

NAGAMANI, S. C., *et al* Clinical spectrum associated with recurrent genomic rearrangements in chromosome 17q12. *Europ. J. Hum. Genet*., v.18, n.3, p. 278-284, 2010.
.
NARISAWA, Y.; HASHIMOTO, K.; KOHDA, H. Perifollicular clear space under skirt-like epithelial structure of human small vellus hair follicle. *J Dermatol Sci*., v.10, n.2, p.110–117, 1995.

OLSEN, E.A. Hypertrichosis. In: OLSEN, E.A. *Disorders of hair growth*: diagnosis and treatment. New York: McGraw-Hill; 1993. p.315-36.

ORENTREICH, N.; DURR, N.P. Biology of scalp hair growth. *Clin Plast Surg*., v.9, n.2, p.197–205, 1982.

OSTERGAARD, E.; *et al***.** Respiratory chain complex I deficiency due to NDUFA12 mutations as a new cause of Leigh syndrome*. J. Med. Genet*., v.48, n.11, p.737-740, 2011.

PARK, A.M.; KHAN, S.; RAWNSLEY, J. Hair Biology: Growth and Pigmentation. *Facial Plast Surg Clin North Am*., v.26, n.4, p.415-424, 2018.

PAUS, R.; COTSARELIS, G. The biology of hair follicles*. N Engl J Med.,*v.341, n.7, p. 491–497, 1999.

PAUS, R.; FOITZIK, K. In search of the “hair cycle clock”: a guided tour. *Differentiation*, v.72, n.9-10, p.489–511, 2004.

PAUS, R.; THEOHARIDES T.C.; ARCK, P.C. Neuroimmunoendocrine circuitry of the

‘brain-skin connection’. *Trends Immunol*., v.27, n.1, p.32–39, 2006.

PAVONE, P.; *et al.* Congenital generalized hypertrichosis: the skin as a clue to complex malformation syndromes. *Ital J Pediatr*., n.55, 2015.

PELED, A.; *et al***.** Mutations in TSPEAR, encoding a regulator of Notch signaling, affect tooth and hair follicle morphogenesis.*PLoS Genet*., v.12, n.10, e1006369, 2016.

PEZZANI, L.; MILANI D.; TADINI, G. Intellectual Disability: When the Hypertrichosis Is a Clue. *J Pediatr Genet*., v.4, n.3, p.154-158, 2015.

PIÉRARD-FRANCHIMONT, C.; PIÉRARD, G.E. Alterations in hair follicle dynamics in women. *BioMed Res. Int.*, 2013.

PINKUS; H. Embryology of hair. In: MONTAGNA, W.; ELLIS, R.A. *The biology of hair growth*. Academic Press, New York, 1958.

POLIZZI A.; *et al*. Hypertrichosis cubiti (hairy elbow syndrome): a clue to a malformation syndrome. *J Pediatr Endocrinol Metab*.,v18,n.10,p.1019-25, 2005.

PROUD, V. K., LEVINE, C.; CARPENTER, N. J. New X-linked syndrome with seizures, acquired micrencephaly, and agenesis of the corpus callosum. *Am. J. Med. Genet*., v.43, p.458-466, 1992.

PUNWANI, D. *et al*. Multisystem anomalies in severe combined immunodeficiency with mutant BCL11B. *New Eng. J. Med*., v.375, p. 2165-2176, 2016.

RAD, A. *et al.* MAB21L1 loss of function causes a syndromic neurodevelopmental disorder with distinctive cerebellar, ocular, craniofacial and genital features (COFG syndrome). *J. Med. Genet*., v.56, p. 332-339, 2019.

RANDALL, V.A. Hormonal regulation of hair follicles exhibits a biological paradox. *Semin Cell Dev Biol*., v.18, n.2, p.274–285, 2007.

RANDALL, V.A. The role of 5*α*-reductase in health and disease. *In*: Sheppard M, Stewart P (eds) Hormones, enzymes and receptors. *Baillières Clin Endocrinol Metabol*., v.8, p.405–431, 1994.

RARE DISEASE DAY. Disponivel em: <https://www.rarediseaseday.org/article/what-is-rare-disease-day>. Acesso em: 8 mar. 2021.

RAUCH, A. *et al*. Previously apparently undescribed autosomal recessive MCA-MR syndrome with light fixation, retinal cone dystrophy, and seizures: the M syndrome. *Am. J. Med. Genet*., v.82, p.194-198, 1999.

RICHTER, T.; *et al.* International Society for Pharmacoeconomics and Outcomes Research Rare Disease Special Interest Group. Rare Disease Terminology and Definitions-A

Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group. *Value Health,* v.18, n.6, p.906-914, 2015.

RICHARD, G.; *et al*. Genetic heterogeneity in erythrokeratodermia variabilis: novel mutations in the connexin gene GJB4 (Cx30.3) and genotype-phenotype correlations. *J. Invest. Derm*., v.120, p.601-609, 2003.

ROBERTSON, S. P.; *et al.* Localized mutations in the gene encoding the cytoskeletal protein filamin A cause diverse malformations in humans. *Nature Genet.*, v.33, p.487-491, 2003.

ROOK, A. Endocrine influences on hair growth. *Br Med J*., v.1, n.5435, p.609–614, 1965.

ROSENFIELD, R.L. Clinical practice. Hirsutism. *N Engl J Med*., v.353, n.24, p.2578–88, 2005.

RUSSELL, D.W.; *et al.* The molecular genetics of steroid 5 alpha-reductases. *Recent Prog Horm Res*., v.49, p.275–284, 1994.

SCHMIDT-ULLRICH, R.; PAUS, R. (2005). Molecular principles of hair follicle induction and morphogenesis. *Bioessays*,v.27, n.3, p.247–261, 2005.

SCHNEIDER, M.R.; SCHMIDT-ULLRICH, R.; PAUS, R. The hair follicle as a dynamic miniorgan. *Curr Biol.*, v.19, n.3, p.132-142, 2009.

SHUKLA, A.; *et al*. Homozygosity for a nonsense variant in AIMP2 is associated with a progressive neurodevelopmental disorder with microcephaly, seizures, and spastic quadriparesis. *J. Hum. Genet*., v.63, p.19-25, 2018.

SLOMINSKI, A.; *et al*. Hair follicle pigmentation. *J Invest Dermatol*., v.124, n.1, p.13–21, 2005.

SOUZA, Í.P.;*et al*. A qualitative approach to rare genetic diseases: an integrative review of the national and international literature. *Cien Saude Colet*., v.24, n.10, p.3683-3700, 2019.

STENN, K. Exogen is an active, separately controlled phase of the hair growth cycle. *J Am Acad Dermatol*, v.52, n.2, p.374–375, 2005.

STENN, K. S.; PAUS R. Controls of hair follicle cycling. *Physiol Rev*, n. 81, v.1, p. 449-94. 2001.

STOCCO DOS SANTOS, R. C.; *et al*. Stocco dos Santos X-linked mental retardation syndrome: clinical elucidation and localization to Xp11.3-Xq21.3. *Am. J. Med. Genet*., v.118A, n.3, p.255-259, 2003.

SZKLARCZYK, D,; *et al*. The STRING database in 2021: customizable protein-protein networks, and functional characterization of user-uploaded gene/measurement sets. Nucleic Acids Res.; 49(D1):D605-D612, 2021.

THOMAS, J.A, *et al*. Immunological and histochemical analysis of regional varia- tions of

epidermal Langerhans cells in normal human skin. *Histochem J*., v.16, n.5, p.507–519, 1894.

TROTTER, M.; DUGGINS, O.H. Age changes in head hair from birth to maturity: index and size of hair of children. *Am J Phys An- thropol*., v.6, n.4, p.489-505, 1948.

TRÜEB, R.M. Causes and management of hypertrichosis. *Am J Clin Dermatol*., v.3, n.9 p.617–27, 2002.

TWIGG, S. R. F.; *et al.* A recurrent mosaic mutation in SMO, encoding the Hedgehog signal transducer smoothened, is the major cause of Curry-Jones syndrome. *Am. J. Hum. Genet*., v.98, p.1256-1265, 2016.

VAN KARNEBEEK, C. D. M.; *et al*. NANS-mediated synthesis of sialic acid is required for brain and skeletal development. *Nature Genet*., v.48, n.7,p. 777-784, 2016. Note: Erratum: Nature Genet. 49: 969 only, 2017.

VAN MATER, D.; *et al*. Transient activation of beta-catenin signaling in cutaneous keratinocytes is sufficient to trigger the active growth phase of the hair cycle in mice. *Genes Dev*., v.17, n.10, p.1219-1224, 2003.

VILJOEN, D.; BEIGHTON, P. Schwartz-Jampel syndrome (chondrodystrophic myotonia). *J. Med. Genet*., v.29, p.58-62, 1992.

VISSERS, L. E. L. M..; *et al*. De novo variants in CNOT1, a central component of the CCR4-NOT complex involved in gene expression and RNA and protein stability, cause neurodevelopmental delay. *Am. J. Hum. Genet.,* v.107, p. 164-172, 2020.

WADE, E. M.; *et al*. Mutations in MAP3K7 that alter the activity of the TAK1 signaling complex cause frontometaphyseal dysplasia. *Am. J. Hum. Genet*., v.99, p.392-406, 2016.
WAFIK, M.; KINI, U. Achalasia-microcephaly syndrome: a further case report. *Clin. Dysmorph*., v.26, p.190-192, 2017.

WENDELIN, D.S.; POPE, D.N.; MALLORY, S.B. Hypertrichosis. *J Am Acad Dermatol*., v.48, n.2, p.161–179, 2003.

WILSON JD.; GRIFFIN, J.E.; RUSSELL, D.W. Steroid 5*α*-reductase 2 deficiency. *Endocr Rev*.,v.14, n.5, p.577–593, 1993.

WITZEL, M.; *et al.* Chromatin-remodeling factor SMARCD2 regulates transcriptional networks controlling differentiation of neutrophil granulocytes. *Nature Genet*., v.49, p.742-752, 2017.

WOO, W.M.; ORO, A.E. Snapshot: hair follicle stem cells. *Cell,* v.146, n.2, p.334-334, 2011.

YUAN, B.; *et al*. Global transcriptional disturbances underlie Cornelia de Lange syndrome and related phenotypes. *J. Clin. Invest*., v.125, p. 636-651, 2015.

ZIVONY-ELBOUM, Y., *et al*. A founder mutation in Vps37A causes autosomal recessive complex hereditary spastic paraparesis**.** *J. Med. Genet*., v.49, n.7, p.462-472, 2012.

ZOUBOULIS, C. C.; *et al*. Sexual hormones in human skin. *Horm Metab Res*., v.39, n.2, p.85–95, 2007.

APÊNDICES

APÊNDICE A

Tabela 5: Categorias de acometimento clínico.

Grupos de acometimento clínico
Herança: autossômica recessiva, autossômica dominante, outra.
Cabeça e pescoço: cabeça, face, orelha, olhos, nariz, boca, pescoço, dente.
Anomalias dentárias: anormalidades dos dentes.
Cardiovascular: coração, vascular.
Geniturinário: genitália externa, interna, rins, ureteres, bexiga.
Esquelético: coluna, membros, pés, mãos, crânio, pelve, articulação.
Sistema nervoso: sistema nervoso central ou periférico.
Deficiência intelectual: diversos graus de deficiência.
Respiratório: vias aéreas, pulmão, insuficiência respiratória, infecção pulmonar.
Abdome: fígado, baço, pâncreas, gastrointestinal
Endocrinologia: diabetes, disfunções tireoidianas, resistência insulínica.
Neoplasia: associação com doença neoplásica maligna.
Óbito precoce: na infância (1-12 anos de idade incompletos)

APÊNDICE B

Tabela 6:Síndromes genéticas com hipertricose.

Syndrome	OMIM	Inheritance	*Gene*	Chromosomal	Clinical features	Reference
Achalasia-microcephaly syndrome	200450	AR	-	-	Achalasia, microcephaly, intellectual disability	WAFIK; KINI, 2017.
Adducted thumbs syndrome	201550	AR	-	-	Congenital cleft palate, microcephaly, craniostenosis and arthrogryposi	KUNZE, *et al.*, 1983.
Agenesis of corpus callosum, cardiac, ocular and genital syndrome	618929	AD	*CDH2*	18q12.1	Global developmental delay and/or intellectual disability, craniofacial dysmophisms.	ACCOGLI *et al.*, 2019
Alazami-yuan syndrome	617126	AR	*TAF6*	7q22.1	Short stature, single transverse palmar crease, microcephaly, dysmorphic facies.	YUAN *et al.*, 2015.
Amaurosis congenita, cone-rod type, with congenital hypertrichosis	204110	AR	-	-	Severe retinal dystrophy characterized by visual impairment from birth and profound photophobia in the absence of night blindness.	JALILI, 1989.
Anemia, congenital hypoplastic, with multiple congenital anomalies/mental retardation syndrome	604315	AR	-	-	Congenital hypoplastic anemia, 'coarse' face, generalized hypertrichosis, multiple anomalies and mental retardation	MORI *et al.*, 1999
Barber-say syndrome	209885	AD	*TWIST2*	2q37.3	Neonatal onset characterized by	MARCHEGIANI, *et al.*, 2015

					congenital generalized hypertrichosis, atrophic skin, ectropion and microstomia.	
Becker nevus syndrome	**604919**	**-**	**-**	**-**	**Epydermal nevus with hyperpigmentation of basal cells**	**HAPPLE; KOOPMAN, 1997**
Beckwith-wiedemann syndrome	**130650**	**AD**	***NSD1***	**11p15.5**	**Variable; exomphalos, macroglossia, gigantism.**	**WEKSBERG *et al.*, 2010**
			KCNQ1	**11p15.5**		
			CDKN1C	**11p15.4**		
Bloom syndrome	**210900**	**AR**	***RECQL3***	**15q26.1**	**Pre- and postnatal growth deficiency, a telangiectatic erythematous rash of the face and other sun-exposed areas, insulin resistance and predisposition to early onset and recurrent cancer of multiple organ systems.**	**ELLIS; GERMAN, 1996.**
Bohring-opitz syndrome	**605039**	**AD**	***ASXL1***	**20q11.21**	**Multiple anomalies: severe intrauterine growth retardation, mental retardation, trigonocephaly, prominent metopic suture, exophthalmos, flexion of the elbows and wrists.**	**HOISCHEN, *et al.*, 2011.**

Cahmr syndrome	**211770**	**AR**	**-**	**-**	**Congenital cataract, generalized hypertrichosis, and intellectual deficit**	**TEMTAMY; SINBAWY, 1991.**
Cantu syndrome	**239850**	**AD**	***ABCC9***	**12p12.1**	**Congenital hypertrichosis, neonatal macrosomia, a distinct osteochondrodysplasia, and cardiomegaly**	**VAN BON *et al.*, 2012**
Cerebellar ataxia, mental retardation and disequilibrium syndrome 2	**610185**	**AR**	***WDR81***	**17p13.3**	**Disequilibrium, intellectual disability.**	**GULSUNER *et al.*, 2011**
Cerebellar, ocular, craniofacial and genital syndrome	**618479**	**AR**	***MAB21L1***	**13q13.3**	**Intellectual disability, characteristic facies, hypoplasia cerebellar**	**RAD *et al.*, 2019**
Cerebral malformation, seizures, hypertrichosis, and overlapping fingers	**213820**	**-**	**-**	**-**	**Multiple congenital anomalies/mental retardation (MCA/MR) syndrome consisting of cerebral malformations, seizures, hypertrichosis, distinctive facies, claw hands, and overlapping fingers**	**MULLER *et al.*, 1993.**
Cerebrooculofascioskeletal syndrome 1	**214150**	**AR**	***ERCC6***	**10q11.23**	**Congenital cataracts, intellectual disability, artrogryposis, microcephaly**	**JAKKOLA *et al.*, 2010**

Cervical hypertrichosis with underlying kyphoscoliosis	**117850**	**AD**	**-**	**-**	**Cutaneous markers of underlying skeletal or neural abnormalities**	**REED, *et al.*, 1989**
Cervical hypertrichosis, anterior cervical	**600457**	**Dominant with paternal age effect**	**-**	**-**	**Anterior cervical hypertrichosis just cephalad to the laryngeal prominence.**	**BRADDOCK, *et al.*, 1995**
Cervical hypertrichosis, congenital anterior cervical, with peripheral sensory and motor neuropathy	**239840**	**AR**	**-**	**-**	**Congenital anterior cervical hypertrichosis with peripheral sensory and motor neurophaty.**	**TRATTNER, *et al.*, 1993**
Chromosome 17q12 deletion syndrome	**614527**	**AD**	***Multiple genes***	**17q12**	**Facial dimorphism, genitourinary anomalies, mental retardation**	**NAGAMI *et al.*, 2010**
Chromosome 17q21.31 duplication syndrome	**613533**	**-**	**-**	**17q21.31**	**Facial dysmorphism, short stature, intellectual disability, prominent incisors**	**GRISART *et al.*, 2009**
Coffin-siris syndro 1, 2, 3, 4, 8 ,9	**135900** **614607** **614608** **614609** **618362** **615866**	**A**	***ARID1B*** ***ARID1A AT*** ***SMARCB1*** ***SMARCA4*** ***SMARCC2*** ***SOX11 SRY-***	**6q25.3** **1p36.11** **22q11.23** **19p13.2** **12q13.2** **2p25.2**	**Multiple malformation syndrome characterized by mental retardation associated with coarse facial features, hypertrichosis, sparse scalp hair, and hypoplastic or absent fifth fingernails or toenails.**	**VERGANO; DEARDORFF, 2014.**
Congenital disorder of glycosylation Iaa, Iq e iie	**617082** **612379** **608779**	**AR**	***NUS1*** ***SRD5A3*** ***COG7***	**6q22.1** **4q12** **16p12**	**Early onset, birth or infancy; multisystem disorder**	**PARK *et al.*, 2014**
Cornelia de lange 1 **3**	**122470** **610759**	**AD**	***NIPBL*** ***SMC3***	**5p13.2** **10q25.2**	**Highly variable phenotype, multisystem malformation, facial**	**ROHATGI *et al.*, 2010**

4	**614701**		***RAD21***	**8q24.11**	**dysmorphism, growth retardation, mental retardation, upper limb anomalies.**	
Corpus callosum, agenesis of, with abnormal genitalia	**300004**	**XL**	***ARX***	**Xp21.3**	**Intellectual disability, seizures, spasticity**	**PROUD *et al.*, 1992**
Cousin syndrome	**260660**	**AR**	***TBX15***	**1p12**	**Congenital dwarfism, hip dislocation, facial dysmorphism**	**COUSIN et al., 1982**
Craniorhiny	**123050**	**AD**	**-**	**-**	**Craniosysnostosis and nasal abnormalities, include hypertrichosis**	**MINDIKOGLU et al., 1991**
Crouzon syndrome	**123500**	**AD**	***FGFR2***	**10q26.13**	**Craniosynostosis causing secondary alterations of the facial bones and facial structure.**	**GLASER *et al.*, 2000**
Curry-jones syndrome	**601707**	**Somatic mosaicism**	***SMO***	**7q32.1**	**Craniosynostosis, polysyndactyly, skin lesions**	**TWIGG et al., 2016**
Dental anomalies and short stature	**601216**	**AR**	***LTBP3***	**11q13.1**	**Significant short stature with brachyolmia and hypoplastic amelogenesis imperfecta with almost absent enamel**	**BERTOLA *et al.*, 2009**
Desanto-shinawi syndrome	**616708**	**AD**	***WAC***	**10p12.1**	**Intellectual disability, dysmorphic facies.**	**DESANTO et al., 2015.**
Developmental and epileptic encephalopathy 57	**617771**	**AD**	***KCNT2***	**1q31.3**	**Intellectual disability, hypotonia, seizures, poor language.**	**MAO *et al*., 2020.**
Developmental and epileptic encephalopathy 85 with or without midline brain defects	**301044**	**XLD**	***SMC1A***	**Xp11.22**	**Refractory seizures, intellectual disability, dysmorphic facies**	**KRUSZKA *et al.*, 2019**
Diabetes mellitus, insulin resistant, with acanthosis nigricans type A	**610549**	**-**	***INSR***	**19p13.2**	**Hypertelorism, prognathism, macroglossia, generalized hypertrichosis, hypertrophy of the clitoris.**	**MARIANI *et al*., 1982**
Diarrhea,	**520100**	**-**	***NDL4,***	**-**	**Early onset,**	**CORMIER-**

chronic, with villous atrophy			***ND5, MTCYB***		**hypertrichosis, cerebellar ataxia, growth retardation, renal insufficiency, bilateral sensorial deafness.**	**DAIRE *et al*., 1994**
Distichiais **Tristichiais**	**126300** **190800**	**AD** **AD**	**-**	**-**	**Double rows of eyelashes.** **Three row of eyelashes.**	**FOX, 1962; DANFORTH, 1925**
Donohue syndrome	**246200**	**AR**	***INSR***	**19p13.2**	**Extreme insulin resistance, characteristic dysmorphic facies lipoatrophy and muscular hypotrophy.**	**CANTANI; ZIRUOLO; TACCONI, 1987**
Dysraphism	**-**	**-**	**-**	**-**	**Lumbar or sacral hypertrichosis, neurologic associations such spina bifida, myelomeningocele.**	**HOLMES; LI, 2019**
Dyssegmental dysplasia, rolland-desbuquois type	**224400**	**AR**	**-**	**-**	**Lethal forms of neonatal short-limbed dwarfism**	**FASANELLI, *et al.*, 1985**
Ectodermal dysplasia 14, hair/tooth type with or without hypohidrosis	**618180**	**AR**	***PSPEAR***	**21q22.3**	**Scalp hypotrichosis and hipodontia.**	**PELED *et al.*, 2016.**
Ehlers-danlos syndrome, dermatosparaxis type	**225410**	**AR**	***ADAMTS***	**5q35.3**	**Multisystem disorder: cardiovascular, neurologic, skeletal, genitourinary anomalies.**	**LAPIERRE; NUSGENS, 1993**
Erythroderma, ichthyosiform, congenital, reticular	**609165**	**AD**	***KRT10***	**17q21.2**	**Islands of normal skin surrounded by erythematous ichthyotix patches in a reticulated pattern**	**KRUNIC *et al.*, 2003**
Erythrokeratodermia variabilis et progressiva 2	**617524**	**AD**	***GJB4***	**1p34.3**	**Persistent plaque-like or generalized hyperkeratosis and transient red patches.**	**RICHARD et al.,**

Facial dysmorphism, hypertrichosis, epilepsy, intellectual/developmental delay, and gingival overgrowth syndrome	**618381**	**AD**	***KCNK4***	**11q13.1**	**Facial dysmorfphism: hypotonic facies, bitemporal narrowing, micrognathia, deep-set eyes, bushy eyebrows and long eyelashes, low-set ears, short deep philtrum, gingival overgrowth, prominent upper and lower vermilion, and everted upper lip**	**BAUER *et al.*, 2018**
Facial hypertrichosis	**134000**	**AD**	**-**	**-**	**Facial hypertrichosis**	**TROTTER; DANFORTH, 1922**
Fibromatosis, gingival, with hypertrichosis and mental retardation	**605400**	**-**	**-**	**-**	**Mental retardation, epilepsy, brachymetacarpalia, hypertrichosis, bulbous short nose, thick floppy ears with abnormal configuration, and gingival hypertrophy**	**GOHLICH-RATMANN *et al.*, 2000**
Filippi syndrome	**272440**	**AR**	***CKAP2L***	**2q14.1**	**Facial dysmorphism, growth retardation, microcephaly, cutaneous syndactyly of finger and toes, intellectual deficit.**	**HUSSAIN *et al.*, 2014**
Floating-harbor syndrome	**136140**	**AD**	***SRCAP***	**16p11.2**	**Facial features, short stature, delayed bone age.**	**LACOMBE et al., 1995.**
Fontaine progeroid syndrome	**612289**	**AD**	***SLC25A24***	**1p13.3**	**Growth retardation, decreased subcutaneous fat tissue, triangular face, widely open anterior fontanel, convex and broad nasal ridge, micrognathia, hypertrichosis, craniosynostosis.**	**WRITZL *et al.*, 2017.** **ROBERTSON, 2005; WADE et al., 2016**

Frontometaphyseal dysplasia 1 e 2	**305620** **617137**	**XLR** **AD**	***FLNA*** ***MAP3K7***	**Xq28** **6q15**	**Skeletal dysplasia, deafness, urogenital abnormalities**	**ROBERTSON, 2005; WADE *et al.*, 2016**
GM-1 gangliosisdosis type 1	**230500**	**AR**	***BLB1***	**3p22.3**	**Variable degrees of neurodegeneration and skeletal abnormalities.**	**SUZUKI *et al.*, 2001**
Hairy ears **Hairy ears, Y-linked**	**139500** **425500**	**AD** **Y-linked**	**-** **-**	**-** **Yq**	**Long hairs growing from the helix of the pinna.**	**KAMALAM; THAMBIAH, 1990; RAO, 1970.**
Hairy elbows	**139600**	**AD**	**-**	**-**	**Appears in infancy and regresses at adolescence – Short stature**	**VISSER, *et al.*, 2002**
Hairy palms and soles	**139650**	**AD**	**-**	**-**	**Thickened hair-bearing skin patches on palms and soles**	**JACK SON, *et al.*, 1975**
Hajdu-cheney syndrome	**102500**	**AD**	***NOTCH2***	**1p12**	**Dysmorphic facies, osteopenia/osteoporosis, short stature.**	**ISIDOR et al., 2011.**
Hennekam lymphangiectasia-lymphedema syndrome 1	**235510**	**AR**	***CCBE1***	**18q21.32**	**Generalized lymphatic dysplasia.**	**ALDERS *et al.*, 2014**
Histiocytosis-lymphadenopathy plus syndrome **H syndrome** **Rosai-dorfman disease, familial**	**602782**	**AR**	***SLC29A3***	**10q22.1**	**Comprises features of 4 histiocytic disorders previously thought to be distinct: Faisalabad histiocytosis, sinus histiocytosis with massive lymphadenopathy, H syndrome, and pigmented hypertrichosis with insulin-dependent diabetes mellitus syndrome.**	**BOLZE, *et al*, 2012**
Hydronephrosis, congenital, with cleft palate, characteristic facies, hypotonia, and mental retardation	**604916**	**-**	**-**	**-**	**Multiple congenital anomalies and craniofacial dysmorphism: synophores, long eyelashes, epicanthus, flat nose bridge, short nose, upturned, long filter, low-set ears, appearance of open mouth, full lower**	**OKATOMOTO *et al.*, 1997**

					lip, cleft palate	
Hypertrichosis, congenital generalized;	307150	XLD	-	Xq27.1	Congenital generalized hypertrichosis	MACIAS-FLORES *et al.*, 1984; SUN *et al.*, 2009; DE RAEVE ; KEYMOLEN, 2011; FANTAUZZO *et al.*, 2012
Hypertrichosis, congenital generalized, with or without gingival hyperplasia;	135400	AR	*ABCA5*	17q24.2-q24.3		
Hypertrichosis lanuginosa congenital;	145700	AD	-	-		
Hypertrichosis universalis congenita, ambras type	145701	AD	-	8q22		
Hypomelanosis of ito	300337	Somatic mosaicism	-	Xp11*	Unilateral or bilateral macular hypopigmented whorls, streaks and patches, eyes abnormalities, mental retardation	WENDELIN; POPE; MALLORY,2003
Intellectual developmental disorder with cardiac defects and dysmorphic facies	618316	AR	*TMEM94*	17q25.1	Global developmental delay with intellectual disability, congenital cardiac malformations and dysmorphic facies.	STEPHEN *et al.*, 2018
Imagawa-matsumoto syndrome	618786	AD	*SUZ12*	17q11.2	Generalized overgrowth, macrocephaly, dysmorphic face.	CYRUS *et al.*, 2019
Immunodeficiency 49	617237	AD	*BCL11B*	14q32.2	Dysmorphic facies, intellectual disability,immuno deficiency	PUNWANI *et al.*, 2016
Joubert syndrome	300804	XLR	*OFD1*	Xp22.2	Cerebellar ataxia, intellectual disability, hypotonia, breathing dysregulation.	COENE *et al.*, 2009
Kabuki syndrome 2	300867	XLD	*KDM6A*	Xp11.3	Congenital mental retardation, postanal dwarfism, facial dysmorphism, short fifth finger, scoliosis, cleft palate	VAN LAARHOVEN *et al.*, 2015
Leigh syndrome	256000	AR Mitochon	*Multiple nuclear*	Multiple	Multisystem disorder, global	LAKE *et al*, 2015

		drial	***and mitochon drial genes***		**developmental delay or regression, hypotonia, ataxia, dystonia, and ophthalmologic abnormalities.**	
Lethal short-limb skeletal dysplasia, al gazali type	**601356**	**AR**	**-**	**-**	**Brachydactyly, dysmorphic facies, sclerotic bones**	**GRIGELIONIENE *et al*., 2011**
Leukodystrophy, hypomyelinating 17	**618006**	**AR**	***AIMP2***	**7p22.1**	**Global developmental delay, intractable seizures.**	**SHUKLA *et al*., 2018**
Liang-wang syndrome	**618729**	**AD**	***KCNMA 1***	**10q22.3**	**Wide heterogeneous phenotype, neurologic dysfunction always present.**	**LIANG *et al.*, 2019**
Lichtenstein syndrome	**246550**	**AR**	**-**	**-**	**Dysmorphic facies, severe osteoporosis, repeated fractures, dental anomalies**	**LICHETENSTEIN, 1972.**
Light fixation seizure syndrome	**603530**	**-**	**-**	**-**	**Retinal cone dystrophy, bluish sclerae, severe developmental delay**	**RAUCH *et al*., 1999.**
Lipodystrophy, congenital generalized, type 2 Bernardinelli-seip	**269700**	**AR**	***BSCL2***	**11q12.3**	**Marked paucity of adipose tissue, extreme insulin resistance, hypertriglyceridemia, hepatic steatosis and early onset of diabetes.**	**GARG, 2004**
Lissencephaly 7 with cerebellar hypoplasia	**616342**	**AR**	***CDK5***	**7q36.1**	**Dysmorphic facies, arthrogryposis, seizures, lack of psychomotor development**	**MAGEN *et al*, 2015**
Lymphedema - hypoparathyroidism syndrome	**247410**	**AR**	**-**	**-**	**Hypertrichosis facial and forehead**	**DAHLBERG, *et al.*, 1983**
Mandibulofacial dysostosis with macroblepharon and macrostomia	**602562**	**Isolated cases**	**-**	**-**	**Hypertrichosis of eyebrows and upper eyelid eyelashes.**	**CORONA-RIVERA, *et al.*, 2013**

Mannosidosis, alpha B, lysosomal	**248500**	**AR**	***MAN2B 1***	**19p13.13**	**Highly variable phenotype, mental retardation, coarse facial features, skeletal abnormalities, hearing impairment, neurologic motor problems, and immune deficiency**	**RIISE STENSLAND *et al.*, 2016**
Marshall-smith syndrome	**602535**	**AD**	***NFIX***	**19p13.13**	**Accelerated skeletal maturation, blue sclerae, mental retardation, respiratory difficulties.**	**ADAM *et al.*, 2005**
Meester-Loeys syndrome	**300989**	**XL**	***BGN***	**Xq28**	**Early onset aortic aneurysm and dissecton, facial dysmorphism, skeletal abnormalities.**	**MEESTER et al., 2017**
Melanocytic nevus syndrome	**137550**	**Somatic mutation**	***NRAS***	**1p13.2**	**Pigmentary skin defects apparent at birth – Associated risk of neoplasia.**	**KINSLER, *et al.*, 2008; KINSLER *et al.*, 2012; KINSLER *et al.*, 2016.**
Mental retardation, autosomal dominant 57	**618050**	**AD**	***TLK2***	**17q23.2**	**Highly variable phenotype, delayed psychomotor development apparent in infancy or early childhood, language delay, and behavioral abnormalities.**	**REIJNDERS *et al.*, 2018**
Mental retardation, autosomal recessive 35	**615162**	**AR**	**-**	**17q21.31-q22**	**Cognitive impairment, hirsutism, dysmorphic facies, and skeletal abnormalities.**	**AL-OWAIN; ALAZAMI; ALKURAYA, 2011**
Mental retardation, microcephaly, epilepsy and coarse face	**601352**	**AR**	**-**	**-**	**Microcephaly, intellectual disability, epilsepsy.**	**BATTAGLIA *et al*, 1996**
Mental retardation, x-linked 99, syndromic, female-restricted	**300968**	**XLD**	***USP9X***	**Xp11.4**	**Multisystem congenital anomalies. Delayed psychomotor**	**REIJNDERS *et al.*, 2016**

					development, intellectual disability, dysmorphic facial features, scoliosis, postaxial polydactyly, cardiac and urogenital anomalies.	
Mental retardation, x-linked, syndromic, chudley-schwartz type	300861	XLR	-	Xq21.33-q23	Intellectual disability, seizures, dysmorphic facies	CHUDLEY *et al*, 1999
Mental retardation, x-linked, syndromic, nascimento type	300860	XLR	*UBE2A*	Xq24	Intellectual disability, myxedematous appearance, dysmorphic facial features: arge head, synophrys, prominent supraorbital ridges, almond-shaped and deep-set eyes, large ears, wide mouth with everted lower lip and downturned lip corners.	BUDNY *et al.*, 2010
Michelin tire baby syndrome	156610	AD	*TUBB*	6p21.33	Skin creases congenital symmetric circumferential, primarily of the limbs.	MALIK *et al.*, 2019.
Mitochondrial complex i deficiency, nuclear type 23	618244	AR	*NDUFA 12*	12q22	Phenotype as Leigh syndrome	OSTERGAARD *et al.*, 2011
Mucopolysaccharidosis type ii	309900	XLR	*IDS*	Xq28	Progressive accumulation of glycosaminoglycans in nearly all cell types, tissues, and organs.	WRAITH *et al.*, 2008; MCKUSICK, 1972; ESPOSITO *et al.*, 2000; MOK; CAO; HEGELE, 2003; SHIPLEY *et al.*, 1993
Iiic	252930	AR	*HGSNAT*	8p11.2-p11.1		
iiid	252940	AR	*GNS*	12q14.3		
Vii	253220	AR	*GUSB*	7q11.21		
Mullerian derivatives, persistence of, with lymphangiectasia and postaxial	235255	AR	-	-	Presence of Müller's duct derivatives (rudimentary uterus, fallopian tubes and atresia	URIOSTE *et al.*, 1993

polydactyly					**vagina) and other genital abnormalities (cryptorchidism, micropenis), intestinal and pulmonary lymphangiectasia, protein-losing enteropathy, hepatomegaly and renal abnormalities.**	
Multicentric osteolysis, nodulosis, and arthropathy	**259600**	**AR**	***MMP2***	**16q12.2**	**Multiple subcutaneous nodules, peripheral osteolysis, which is usually limited to the hands and feet, osteoporosis**	**ZANKL *et al.*, 2007**
Neurodevelopmental disorder with progressive microcephaly, spasticity, and brain anomalies	**617527**	**AR**	***PLAA***	**9p21.2**	**Infantile onset of progressive microcephaly, spasticity, severe global developmental delay, mental retardation, severely impaired or absent motor function, seizures and optic atrophy.**	**HALL *et al.*, 2017**
Nevoid hypertrichosis	**-**	**-**	**-**	**-**	**Congenital single or multiple patches of terminal hair on skin.**	**GUPTA *et al.*, 2003**
Oliver-Mcfarlane syndrome	**275400**	**AR**	***PNPLA6***	**19p13**	**Trichomegaly, severe chorioretinal atrophy and growth hormone deficiency, hypogonadotropic hypogonadism, thyroid-stimulating hormone deficiency.**	**HUFNAGEL *et al.*, 2015**
Perching syndrome	**617055**	**AR**	***KLHL7***	**7p15.3**	**Dysmorphic facies, intellectual disability, feeding and breathing difficulties**	**KANTHI*et al,* 2019.**
Polythelia pilosa	**-**	**-**	**-**	**-**	**Single of multiple tufts of hair occur along the mammary line.**	**CAMACHO, *et al.*, 1998**
Pontocerebellar hypoplasia type 8	**614961**	**AR**	***CHMP1A***	**16q24.3**	**Abnormal movements, hypotonia,**	**MOCHIDA *et al.*, 2012**

					spasticity, visual defects.	
Porphyria cutanea tarda i, ii	**176090 176100**	**AD – AR**	***UROD***	**1p34.1**	**The most common type of porphyria, onset of light-sensitive dermatitis in later adult life, associated with the excretion of large amounts of uroporphyrin in urine.**	**LAMBRECHT; THAPAR; BONKOVSKY, 2007; DESNICK; ASTRIN, 2002; FRANK *et al.*, 1998**
Porphyria, congenital erythropoietic	**263700**	**AR**	***UROS***	**10q26.2**		
Variegate porphyria	**176200**	**AD**	***PPOX***	**1q23.3**		
Primary multifocal localized hypertrichosis	**-**	**-**	**-**	**-**	**Congenital hypertrichosis**	**GARCIA-HERNANDEZ, *et al.*, 2001**
Ramon syndrome	**266270**	**AR**	**-**	**-**	**Kerubism: maxillary fibrous dysplasia: bilateral and painless facial edema that extends from the mandible to the lower orbital margins, gingival fibromatosis, epilepsy, mental deficiency, and growth developmental delay**	**RAMON; BERMAN; BUBIS, 1967**

Rubinstein-taybi syndrome i, ii	**180849** **613684**	**AD** **AD**	***CREBBP*** ***EP300***	**16p13.3** **22q13.2**	**Multiple congenital anomaly syndrome characterized by mental retardation, postnatal growth deficiency, microcephaly, broad thumbs and halluces, and dysmorphic facial features**	**HENNEKAM, 2006**
Sandestig-stefanova syndrome	**618804**	**AR**	***NUP188***	**9q34.11**	**Pre- and postnatal microcephaly, trigonocephaly, congenital cataract, microphthalmia, facial gestalt, camptodactyly**	**SANDESTIG *et al.*, 2019**
Schinzel-giedion midface retraction syndrome	**269150**	**AD**	***SETBP1***	**18q12.3**	**Mental retardation, typical facial changes: prominent forehead, retraction of the middle face and short, upturned nose, multiple congenital malformations including skeletal, genitourinary and cardiac and a higher prevalence of tumors, mainly neuroepithelial.**	**HOISCHEN *et al.*, 2010**
Schwartz-jampel syndrome	**255800**	**AR**	***HSPG2***	**1p36.12**	**Dysmorphic facies, skeletal abnormalities, osteoporosis, pigeon breast, blepharophimossis, joint contractures**	**VILJOEN; BEIGHTON, 1992.**
Seckel syndrome 9	**616777**	**AR**	***TRAIP***	**3p21.31**	**Intrauterine growth retardation, dwarfism, microcephaly, mental retardation and a characteristic "bird's head" facial appearance**	**SILENGO *et al.*, 2001**

Segmental odontomaxillary dysplasia	**-**	**-**	**-**	**-**	**Unilateral enlargement of maxillary alveolar bone and gingiva.**	**GONZALEX-ARRIAGADA, *et al.*, 2012**
Sialuria	**269921**	**AD**	***GNE***	**9p13.3**	**Hepatoplenomegaly, dysmorphic facies, developmental delay.**	**ENNS *et al.*, 2001**
Spastic paraplegia 53, autossomal recessive	**614898**	**AR**	***VPS37A***	**8p22**	**Early-onset spastic paraplegia, with spasticity in the lower limbs that progresses to the upper extremities**	**ZIVONY-ELBOUM *et al.*, 2012**
Specific granule deficiency 2	**617475**	**AR**	***SMARCD2***	**17q23.3**	**Recurrent infections, skeletal abnormalities, dental anomalies**	**WITZEL *et al.*, 2017**
Spinocerebellar ataxia, autosomal recessive 20	**616354**	**AR**	***SNX14***	**6q14.3**	**Delayed psychomotor development, speech impaired or absent, gait with a broad or absent base, gross facies and cerebellar atrophy.**	**THOMAS *et al.*, 2014**
Spinocerebellar ataxia 42, eraly-onset, severe, with neurodevelopmental deficits	**618087**	**AD**	***CACNA1G***	**17q21.33**	**Intellectyal disability, dysmorphic facies, cerebellar ataxia,**	**CHEMIN *et al.*, 2018**
Spondyloepimetaphyseal dysplasia genevieve type	**610442**	**AR**	***NANS***	**9q22.33**	**Intellectual disability, skeletal dysplasia.**	**VAN KARNEBEEK et al., 2016.**
Stocco dos santos x-linked mental retardation syndrome	**300434**	**XL**	***SHROOM4***	**Xp11.22**	**Intellectual disability, poor or absent speech, hip luxation, short stature,**	**STOCCO DOS SANTOS *et al.*, 2003.**
Sweeney-cox syndrome	**617746**	**AD**	***TWIST1***	**7p21.1**	**Facial dysostosis**	**KIM *et al.*, 2017**
Tenorio syndrome	**616260**	**AD**	***RNF125***	**18q12.1**	**Excessive growth, macrocephaly and**	**TENORIO *et al.*, 2014**

					intellectual deficit. Some patients may have hydrocephaly hypoglycemia and inflammatory diseases resembling Sjogren's syndrome.	
Trichohepatoneurodevelopmental syndrome	**618268**	**AR**	***CCDC47***	**17q23.3**	**Complex multisystem disorder: woolly hair, dysmorphic features, liver disfunction, hypotonia, several global developmental delay.**	**MORIMOTO, *et al.*, 2018**
Trichomegaly	**190330**	**AR**	***FGF5***	**4q21.21**	**Prolonged anagen phase of the hair follicles of the eyelashes, which leads to excessive growth, but may be associated with hypertrichosis in other regions of the face and body**	**HIGGINS *et al.*, 2014**
Vissers-bodmer syndrome	**619033**	**AD**	***CNOT1***	**16q21**	**Variable intellectyal disability, behavioral abnormalities**	**VISSERS et al., 2020**
Warburg micro syndrome 1	**600118**	**AR**	***RAB3GAP***	**2q21.3**	**Facial hypertrichosis, microcefphaly, microphthalmia, congenital cataracts, severe mental retardation, hypogonadism.**	**WARBURG, *et al.*, 1993**
Wiedemann-steiner syndrome	**605130**	**AD**	***KMT2A***	**11q23.3**	**Cubiti hypertrichosis that appears in childhood and regresses in adolescence, associated with short stature, facial changes that become more apparent with age: long eyelashes, thick and arched eyebrows with lateral enlargement, wide nasal bridge and slanted and**	**MIYAKE *et al.*, 2016**

					downward eyelid fissures; intellectual disability, behavioral difficulties and generalized hypertrichosis.	
Zimmermann-laband syndrome 1	**135500**	**AD**	***KCNH1***	**1q32.2**	**Gingival fibromatosis, dysplastic or absent nails, hypoplasia of the distal phalanges, scoliosis, hepatosplenomegaly, among others.**	**BALASUBRAMANIAN; PARKER, 2010**

AD: autosomal dominant; AR: autosomal recessive; OMIM: Online Mendelian Inheritance in Man.